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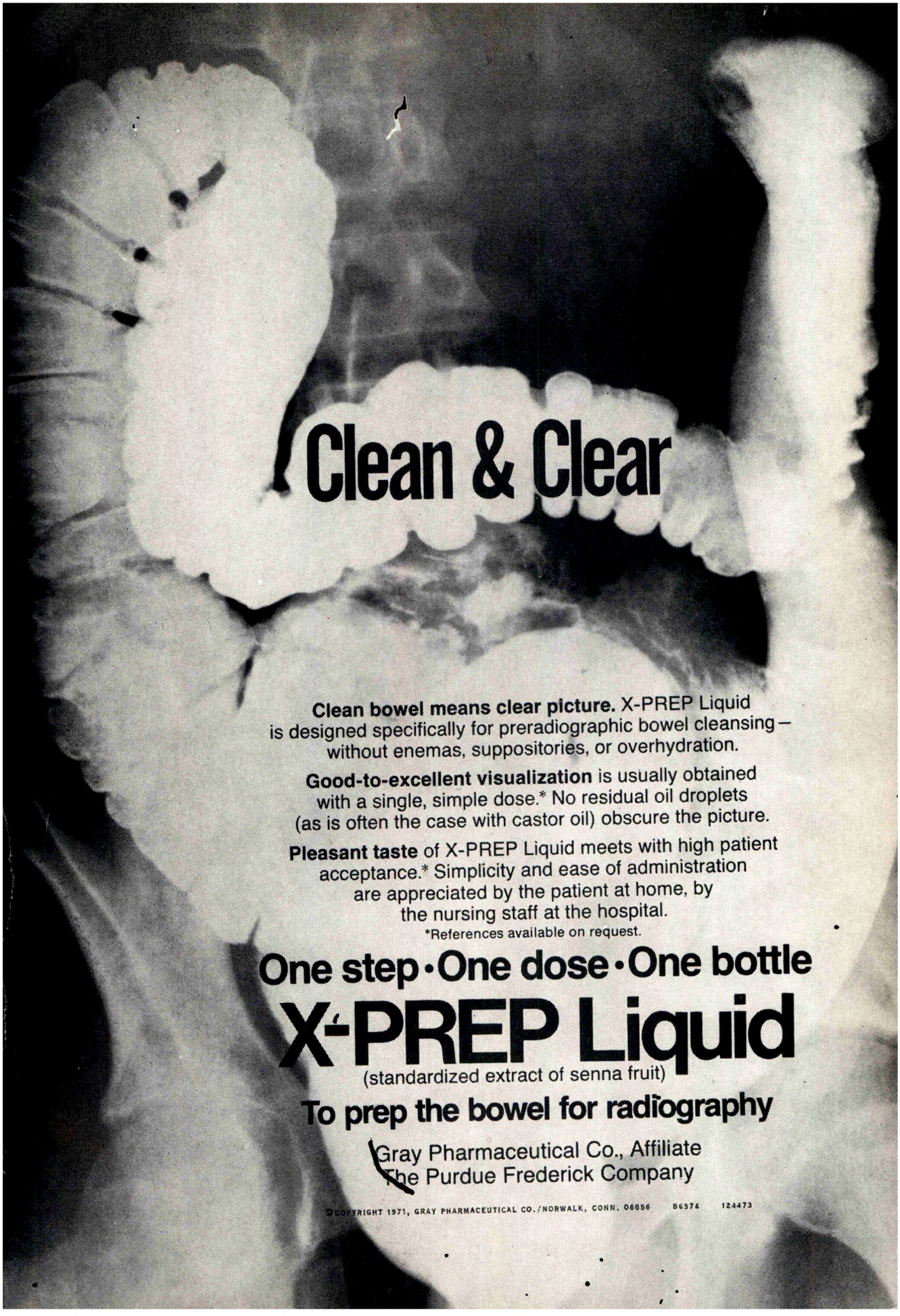

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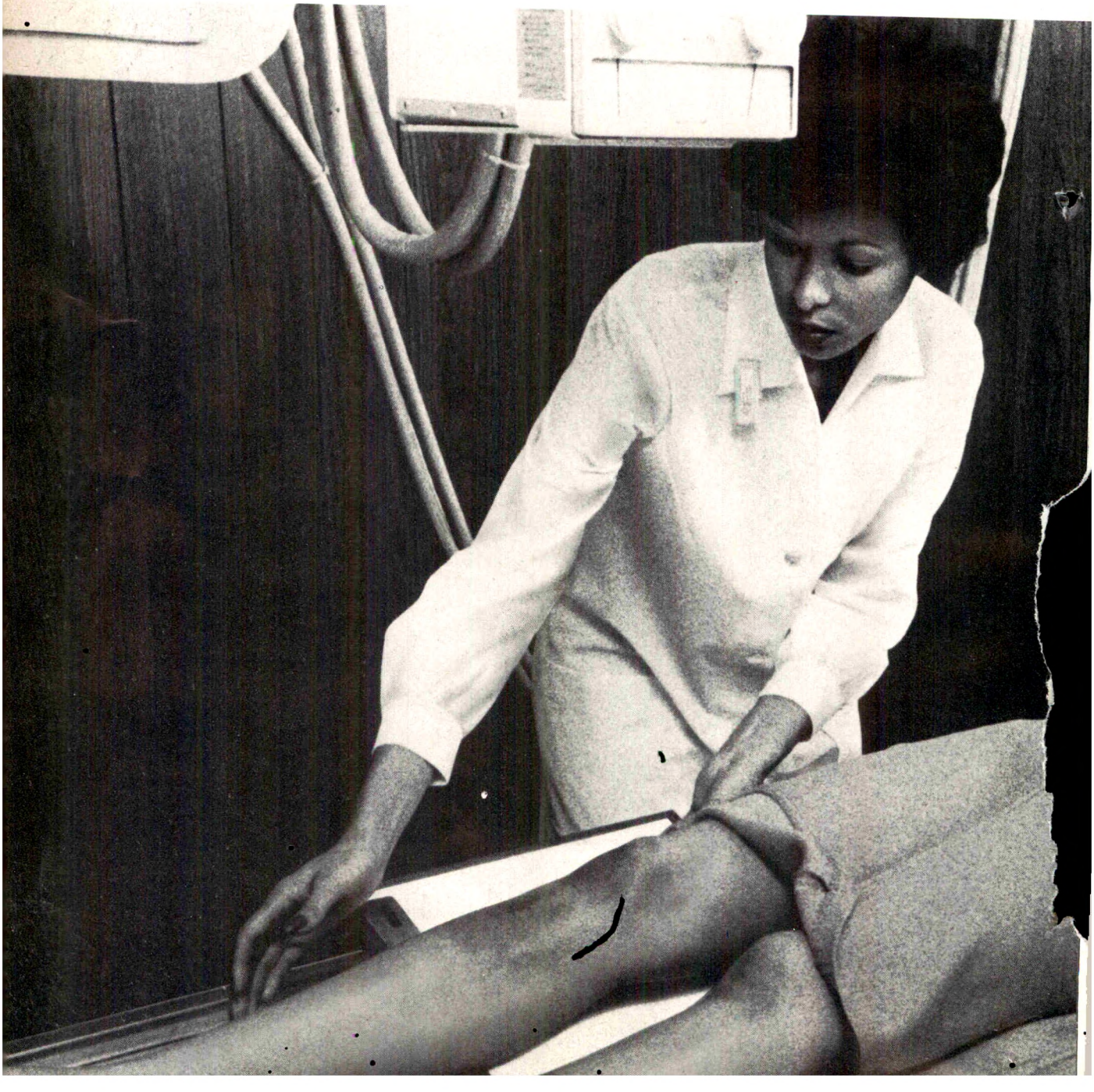

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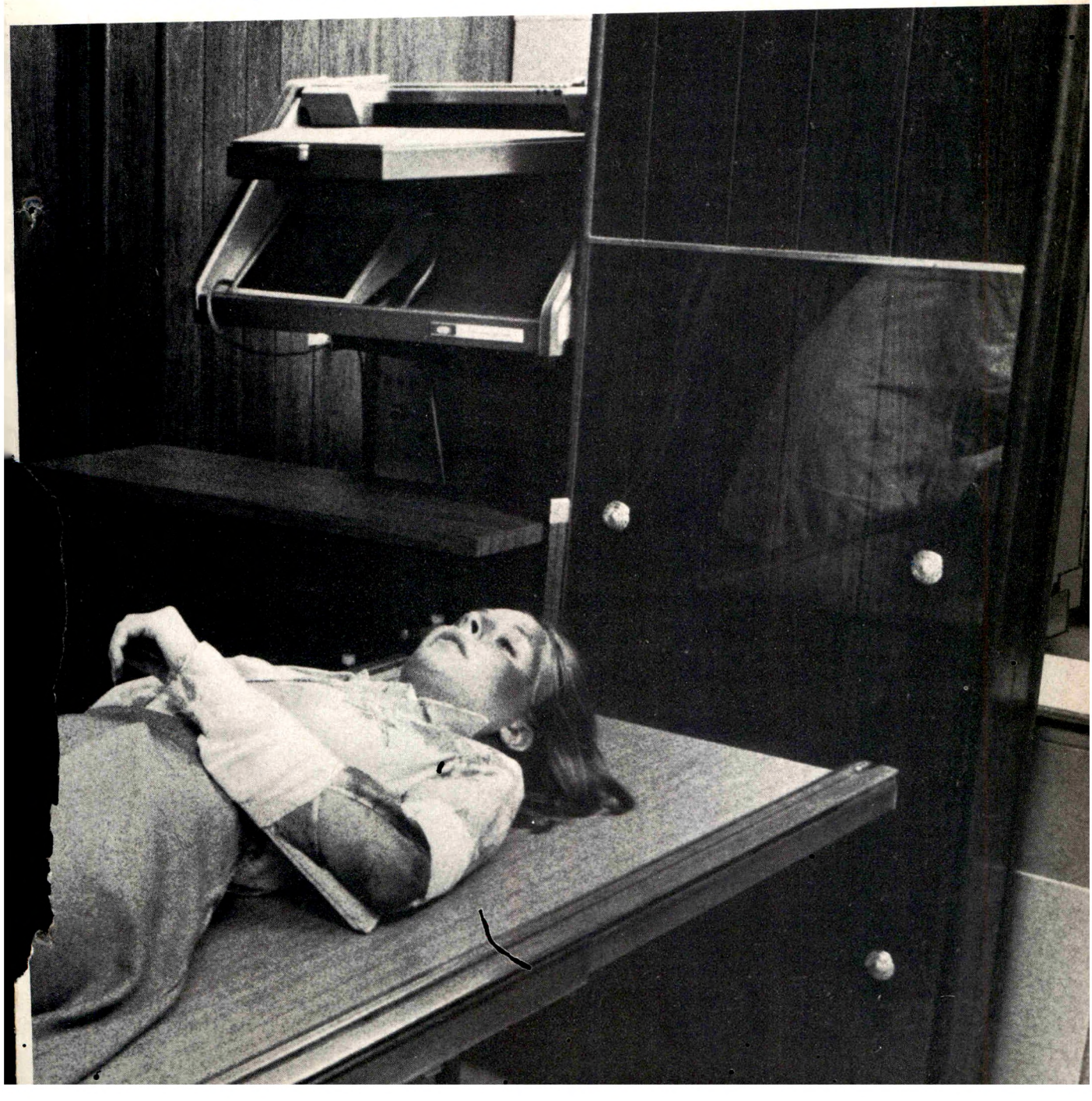

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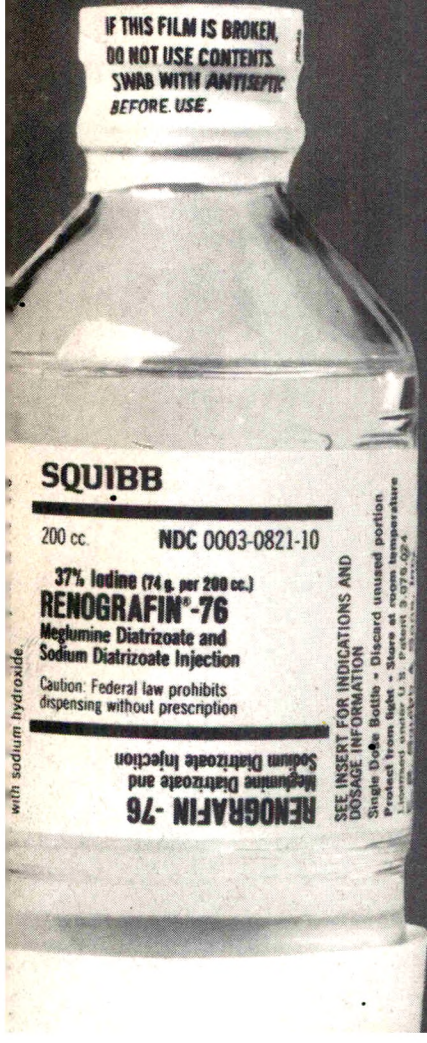

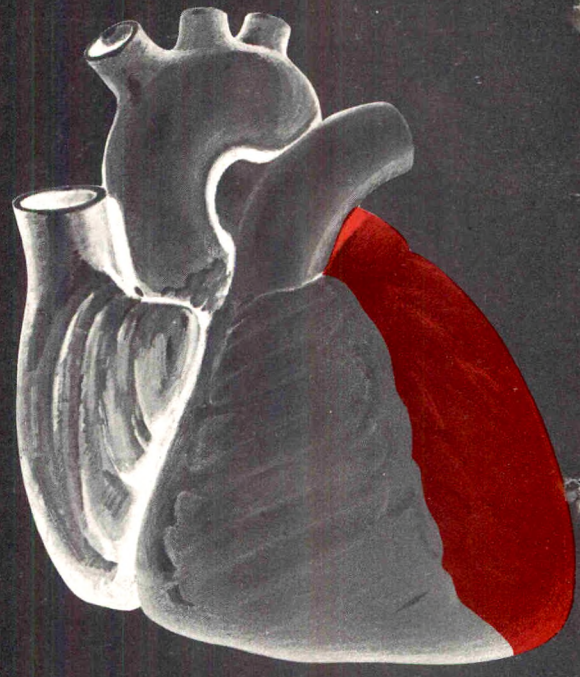

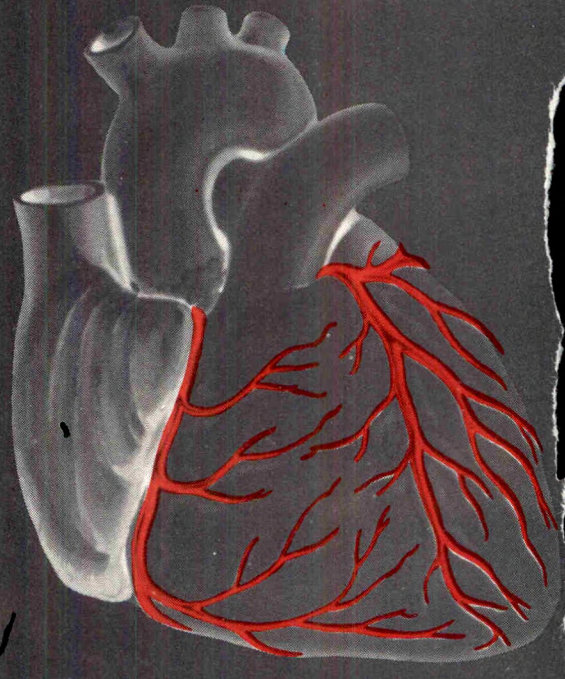

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Contraindications: In patients with a hypersensitivity to salts of diatrizoic acid. Urography contraindicated in patients with anuria.

Warnings: A definite risk exists with the use of contrast agents in excretion urography in patients with multiple myeloma. There has been uria with progressive uremia, renal failure and death. This risk of the procedure in these tients is not a contraindication; however, rtial dehydration in preparation for study is t recommended since it may predispose for ecipitation of myeloma protein in renal bules. No therapy, including dialysis, has en successful in reversing this effect. yeloma should be considered in persons over before undertaking urographic procedures.

In cases of known or suspected pheochromocytoma, if the physician feels that the possible benefits outweigh the considered risks, diopaque materials should be administered h extreme caution; however, an absolute nimum of material should be injected, the od pressure should be assessed throughout procedure, and measures for treating a pertensive crisis should be available.

Contrast media may promote sickling in nozygous individuals when injected I.V. or a-arterially. Although a history of sensitivity odine *per se* or to other contrast media is an absolute contraindication, administra- of diatrizoate requires extreme caution in h cases. Renografin-76 should be used in gnant patients only when the physician ms its use essential to the welfare of the ent since safe use during pregnancy has been established. Perform thyroid function s prior to administration of Renografin-76 e iodine-containing contrast agents may r the test results.

eigh the inherent risks against necessity performing *angiocardiography* in cyanotic nts and patients with chronic pulmonary hysema. In *pediatric angiocardiography*, a e of 10 to 20 cc. may be particularly hazus in infants weighing less than 7 kg.; this is probably significantly increased if these nts have preexisting right heart "strain," heart failure, and effectively decreased bliterated pulmonary vascular beds. Per- *urography* with extreme caution in per- with severe concomitant hepatic and disease. Perform *selective coronary argraphy* only in selected patients and those hom expected benefits outweigh the proral risk.

Cautions: Diagnostic procedures involving of contrast agents should be performed r the direction of personnel with prereqe training and a thorough knowledge of the cular procedure. Appropriate facilities d be available for coping with situations n may arise as a result of the procedure for emergency treatment of severe re- ns to the contrast agent itself; competent nnel and emergency facilities should be able for at least 30 to 60 minutes after I.V. nistration since delayed reactions have known to occur. These severe life- tening reactions suggest hypersensitivity contrast agent. A personal or family his- f asthma or allergy or a history of

special attention and may predict more accurately than pretesting the likelihood of a reaction although not the type nor severity of the reaction in the individual. The value of any pretest is questionable. The pretest most performed is the slow I.V. injection of 0.5 to 1.0 cc. of the preparation prior to injection of the full dose; however, the absence of a reaction to the test dose does not preclude the possibility of reaction to the full diagnostic dose. Should the test dose produce an untoward response, the necessity for continuing the examination should be re-evaluated. If deemed essential, examination should proceed with all possible caution. In rare instances, reaction to the test dose may be extremely severe; therefore, close observation and facilities for emergency treatment are indicated.

Renal toxicity has been reported in a few patients with liver dysfunction who were given oral cholecystographic agents followed by urographic agents; therefore, if known or suspected hepatic or biliary disorder exists, administration of Renografin-76 should be postponed following the ingestion of cholecystographic agents. Consider the functional ability of the kidneys before injecting Renografin-76. Use cautiously in severely debilitated patients and in those with marked hypertension. Bear in mind the possibility of thrombosis when using percutaneous techniques.

In *excretion urography*, adequate visualization may be difficult or impossible in uremic patients or others with severely impaired renal function (see Contraindications). In *aortography* repeated intra-aortic injections may be hazardous; this also applies to *pediatric angiocardiography* particularly in infants weighing less than 7 kg. (see Warnings). In *peripheral arteriography*, hypotension or moderate decreases in blood pressure seem to occur frequently with intra-arterial (brachial) injections; this is transient and usually requires no treatment. Monitor blood pressure during the immediate 10 minutes after injection. It is recommended that *selective coronary arteriography* not be performed for about 4 weeks after diagnosis of myocardial infarction; mandatory prerequisites to this procedure are experienced personnel, ECG monitoring apparatus, and adequate facilities for immediate resuscitation and cardioversion.

Adverse Reactions: Nausea, vomiting, flushing, or a generalized feeling of warmth are the reactions seen most frequently with intravascular injection. Symptoms which may occur are chills, fever, sweating, headache, dizziness, pallor, weakness, severe retching and choking, wheezing, a rise or fall in blood pressure, facial or conjunctival petechiae, urticaria, pruritus, rash, and other eruptions, edema, cramps, tremors, itching, sneezing, lacrimation, etc. Antihistaminic agents may be of benefit; rarely, such reactions may be severe enough to require discontinuation of dosage. There have been a few reports of a burning or stinging sensation or numbness, of venospasm or venous pain, and of partial collapse of the injected vein. Neutropenia or thrombophlebitis may occur. Severe reactions which may require emergency measures (see Precautions) are a possibility and include cardiovascular reaction characterized by peripheral vasodilatation with hypotension and reflex tachycardia, dyspnea, agitation, confusion, and cyanosis progressing to unconsciousness. An allergic-like reaction ranging from rhinitis or angioneurotic edema to laryngeal or bronchial spasm or anaphylactoid shock may occur. Temporary renal shutdown or other nephropathy may occur.

Adverse reactions as a consequence of *excretion urography* include cardiac arrest, ventricular fibrillation, anaphylaxis with severe asthmatic reaction, and flushing due to generalized vasodilation. Risks of *aortography* procedures include injury to aorta and neighboring organs, pleural puncture, renal damage (including infarction and acute tubular necrosis

procedure in presence of preexistent renal disease, retroperitoneal hemorrhage from translumbar approach, spinal cord injury and pathology associated with syndrome of transverse myelitis, generalized petechiae, and death following hypotension, arrhythmia, and anaphylactoid reactions. In *pediatric angiocardiography*, arrhythmia and death have occurred. During *peripheral arteriography*, hemorrhage from puncture site, thrombosis of the vessel, and brachial plexus palsy (following axillary artery injection) have occurred. During *selective coronary arteriography* and *selective coronary arteriography with left ventriculography*, transient ECG changes (most patients); transient arrhythmias (infrequent); ventricular fibrillation (from manipulation of catheter or administration of medium); hypotension; chest pain; myocardial infarction; transient elevation of creatinine phosphokinase (occurred in about 30% of patients tested); fatalities have been reported; hemorrhage, thrombosis, pseudoaneurysms at puncture site, dislodgment of arteriosclerotic plaques, dissection of coronary vessels, and transient sinus arrest have occurred due to the procedure.

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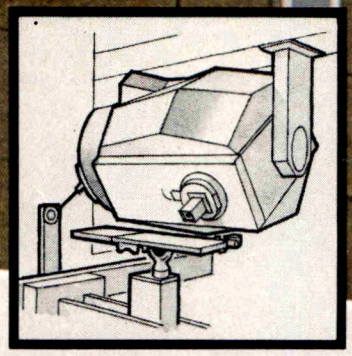

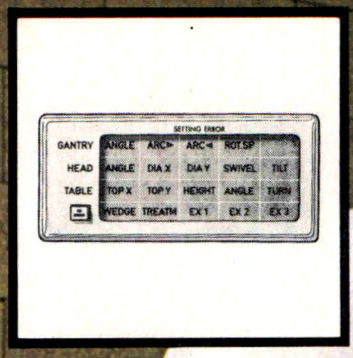

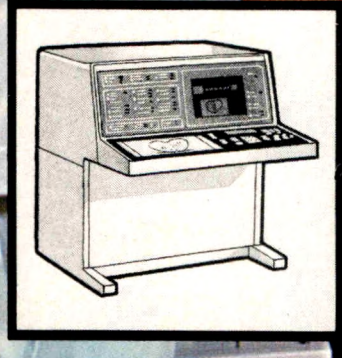

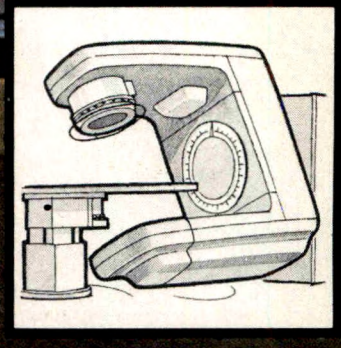

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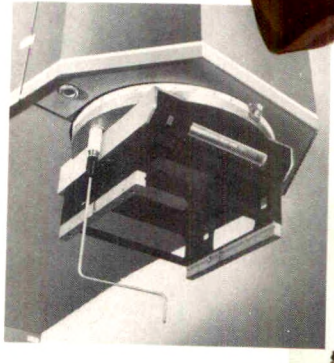

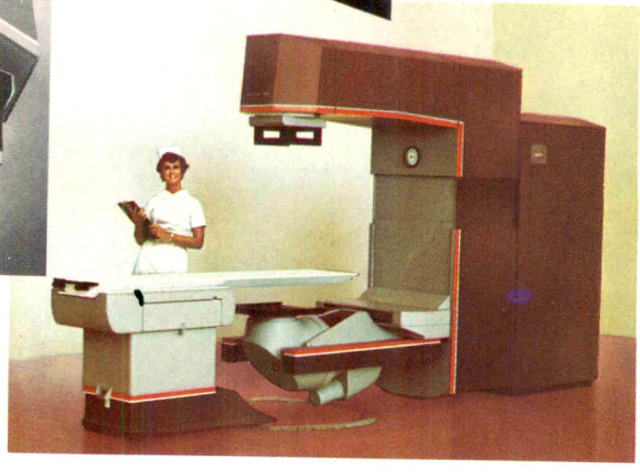

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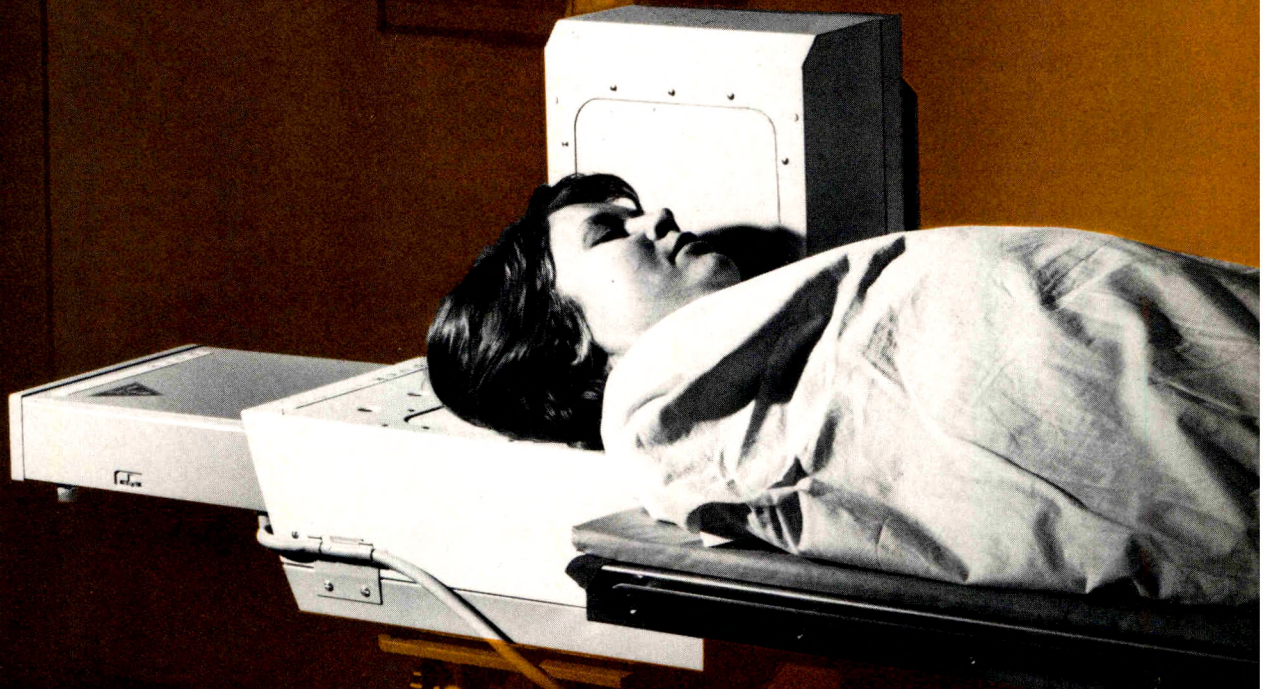

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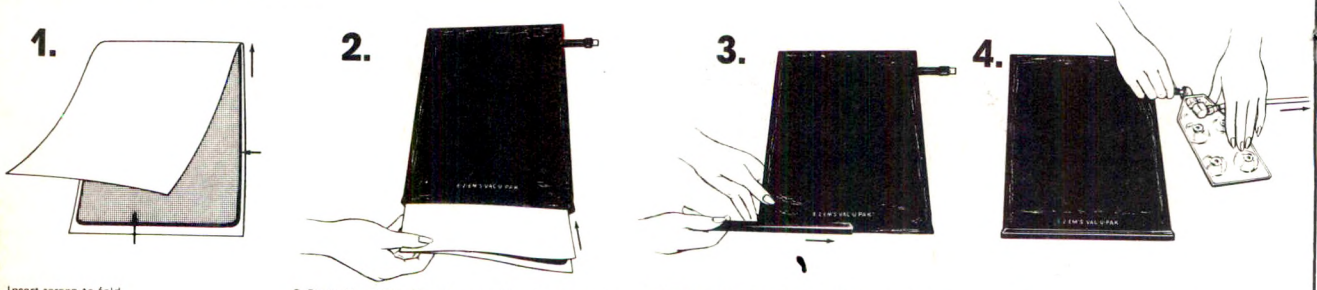

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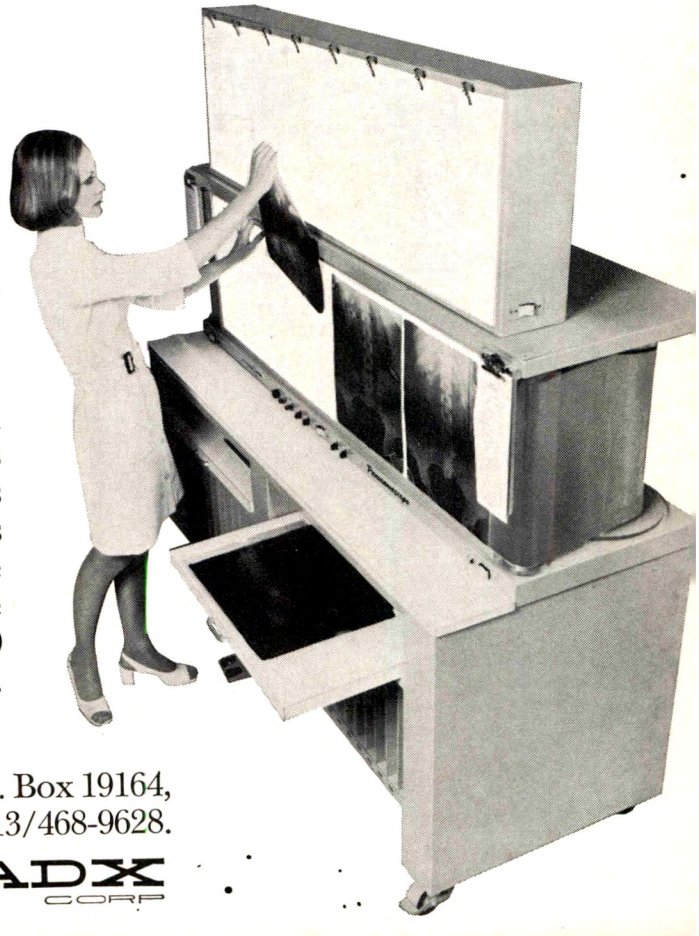

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INDICATIONS AND ALTERNATIVES IN X-RAY DIAGNOSIS: A Guide to the Effective Employment of Roentgenologic Studies in the Solution of Diagnostic Problems (2nd Ed.) *by* **Melvyn H. Schreiber,** *Univ. of Texas Medical Branch, Galveston.* The material included in this book has been the basis for the teaching of medical students, house officers and general physicians for several years. It has been revised and updated frequently. This illustrated volume describes and depicts the various kinds of roentgenologic examinations available for the unravelling of diagnostic problems. The book is divided into chapters based upon organ systems and common abnormalities are illustrated. Emphasis is on providing the reader with a thorough background in the uses to which the ordinary and special x-ray studies may be put, with alternatives emphasized when indicated examination cannot be performed or when more than one kind of examination is available for the solution of a specific problem. Indication and contraindications are carefully defined. The volume is ideal as a textbook for the core courses in diagnostic roentgenology for medical students. Mastery of its contents will permit students beginning their intensive ward and clinic experience to select the appropriate diagnostic roentgenologic examination according to the indications presented by the patient. Moreover, a certain facility in film interpretation and differential diagnosis will come with a study of this text. The organ system chapters can rapidly be consulted for the kinds of examination available for study of symptom complexes of the patient. The other large group of people for whom this work has been especially prepared is interns and residents in fields other than radiology. As a reference work to aid in the planning of diagnostic workup this volume will be found especially handy, and its use will serve to reduce the number of non-indicated examinations ordered while pinpointing the patient's problem early in the diagnostic workup. *'74, 192 pp., 98 il., $11.50, paper*

FOREIGN MEDICAL GRADUATES IN AMERICA *by* **Patricio R. Mamot,** *Ball State Univ., Muncie, Indiana.* This book is designed to provide medical educators in the United States and abroad with the most up-to-date picture of the role of foreign medical graduates in providing medical care to Americans. It underscores the inadequacies of American medical education in accommodating foreign medical graduates; particularly noted are some of the archaic and inadequate structures and functions of the medical schools and the need for the immediate implementation of a sound and coherent policy for the expansion of medical facilities and the increase of enrollment in medicine. The author discusses the ECFMG requirement, its pertinent aspects and the controversies surrounding it; English examination and other language problems; and controversial aspects of medical licensing of foreign medical doctors in the United States. Ample reasons are provided as to why foreign medical graduates are indeed fast becoming a part of the professional and academic mainstream of American medicine. The most currently available statistical information is cited. *'74, 196 pp., $8.50*

ECONOMICS AND HEALTH CARE *by* **Hirsch S. Ruchlin,** *City Univ. of New York, New York, and* **Daniel C. Rogers,** *Agency for International Development, Washington, D. C.* This presentation presumes no previous knowledge of economics on the part of the reader and aims at preparing the reader to better understand the growing literature in the health economics field. The purpose of the book is to introduce and acquaint current and prospective health administrators and planners with basic economic concepts as they relate to the health field. Among the topics presented are the national income accounts, the Consumer Price Index and the Medical Care Price Index, demand theory, production and cost analysis, investment theory, economic growth and health, and financing of health care services. A discussion of the financing of health-related services, an overview of the United States tax structure and its effect on providing health care services, and a brief summary of various alternative financing plans to improve both the financial situation and the economic efficiency of the health industry are also presented. *'73, 336 pp., 23 il., 47 tables, $14.95*

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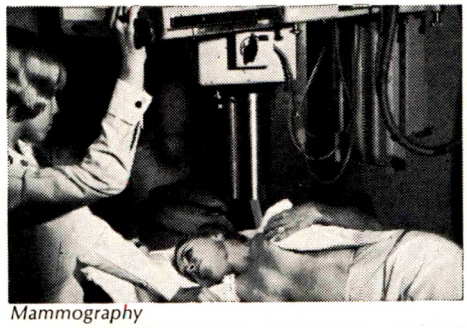

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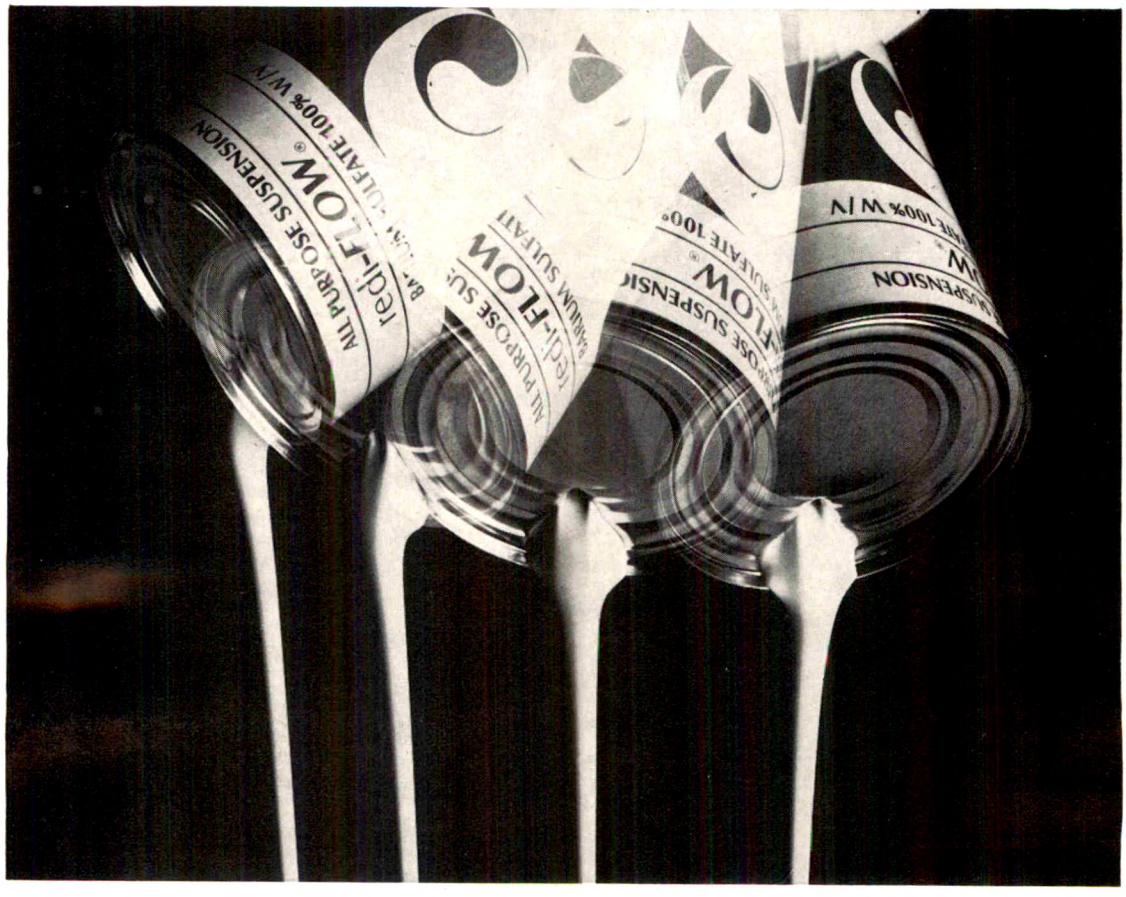

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VOL. 123, NO. 1

LATE RECURRENCE IN MEDULLOBLASTOMA*

By GERALD A. KING, M.D., *and* ROBERT H. SAGERMAN, M.D.
SYRACUSE, NEW YORK

MEDULLOBLASTOMA was first described as an entity distinguishable from other sarcomas and posterior fossa gliomas by Bailey and Cushing in 1925.[1] Medulloblastoma comprises approximately 20 per cent of intracranial tumors in patients under the age of 15 years and is rare in adults. Surgery as sole treatment has not given good results, as the tumor can rarely be excised and the neurologic deficit attending such an attempt may be great. Thus, most papers discuss treatment by surgery and radiotherapy and survival rates are given for 2, 3 or 5 years.[2,3,6–11]

Despite the implication equating short term survival (<5 years) with cure, little long term information is available. Recent experience with 3 late recurrences causing death prompted our review of the literature and the presentation of this report, which illustrates 2 exceptions to Collins' rule.[5]

PATIENT MATERIAL

Thirty-two patients with a diagnosis of medulloblastoma are listed in the Upstate Medical Center Cancer Registry from 1960 through 1972. This registry serves the metropolitan Syracuse, New York area with a population of approximately 500,000. All but 6 of these patients were seen in the Radiation Therapy Division. The 6 had a mean survival of 1 month from the time of diagnosis, 4 of them dying within 1 month, 1 at 1 month and 1 living for 5 months. These cases were not referred to the Radiation Therapy Division because of postoperative problems. Those patients not referred for radiotherapy were seen during the earlier years of this study. In recent years, all patients have been seen by the radiotherapists regardless of their clinical and postoperative conditions.

Of the 26 patients referred for radiotherapy, we have excluded 2 from consideration here, 1 because he was a failure of previous treatment carried out elsewhere and was seen for palliative irradiation only, and the other because there was no histological proof of the nature of the neoplasm. Twenty-four patients remain for analysis, 12 males and 12 females for a male–female ratio of 1:1.

1. The age and sex distributions are shown in Figure 1.

Over the time span considered in this study, the treatment techniques and equipment have undergone a considerable evolution. The first 2 patients were treated with an orthovoltage apparatus, treating posterior fields to the spine and cranial contents with booster doses anteriorly to the head. Twenty patients in this report were treated with a cobalt 60 unit at 120 cm. SSD. Posterior fields to the spine with careful dosimetry and moving match lines were used. The cranial contents were treated with anteroposterior fields with the patient's head angled so as to avoid the orbits. Figure 2 shows a typical dose distribution for this treatment technique. The majority of patients received doses in the order of 5,000 rads to the posterior fossa with between 3,000 and 5,000 rads to the remainder of the central nervous system. The 2 most recent patients have been treated with a modification of this technique (Fig. 3), using opposed lateral fields to the cranial contents and upper cervical spine and posterior fields for the remainder of spinal axis. The current dose schedule delivers 3,500 rads to the entire cerebrospinal fluid (CSF) axis over 4–4½ weeks using 5 fractions per week followed by a booster dose to the posterior fossa and any

* Presented at the Fifty-sixth Annual Meeting of the American Radium Society, Maui, Hawaii, April 21–25, 1974.
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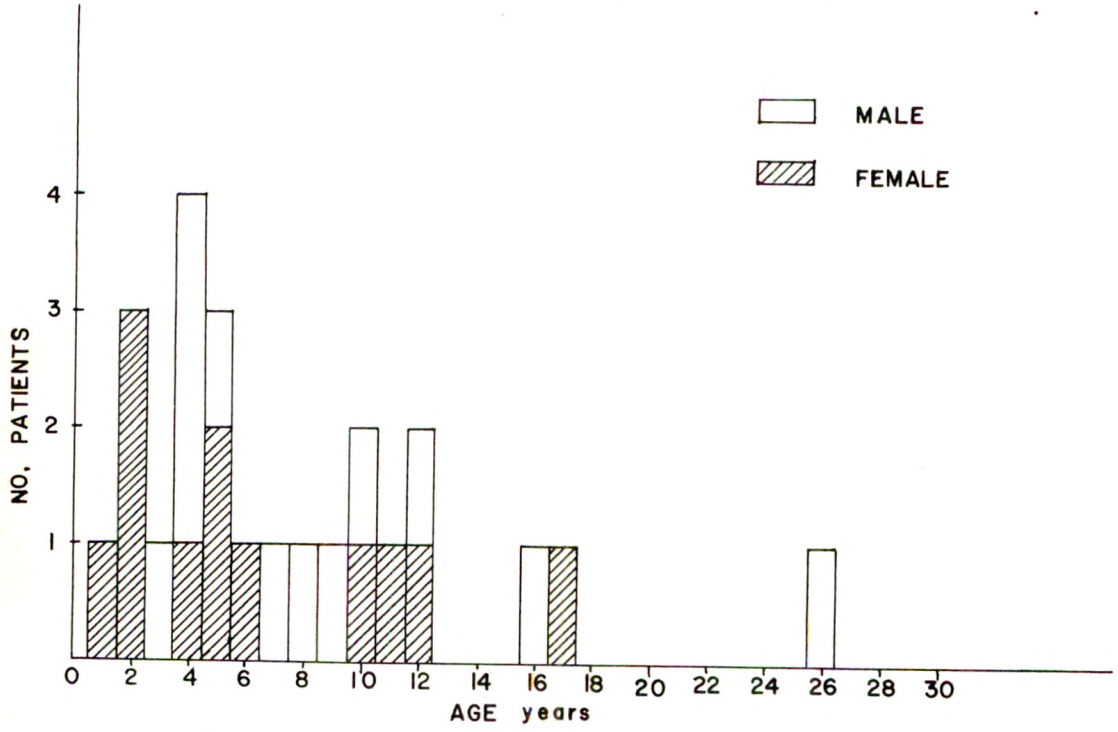

FIG. 1. Age and sex distributions. Numbers of patients *vs.* age at diagnosis.

other known disease of 1,500 rads in 7 fractions over 1½ weeks.

RESULTS

The over-all Berkson-Gage survival curve for these patients is presented in Figure 4 and illustrates a 43 per cent, 3 year survival and a 38 per cent, 5 year survival. Figure 5 shows the status of all patients (except 1 adult).

Postoperative radiation treatment has been generally well tolerated. The patients have anticipated complete temporary epilation in the treatment fields. Four patients

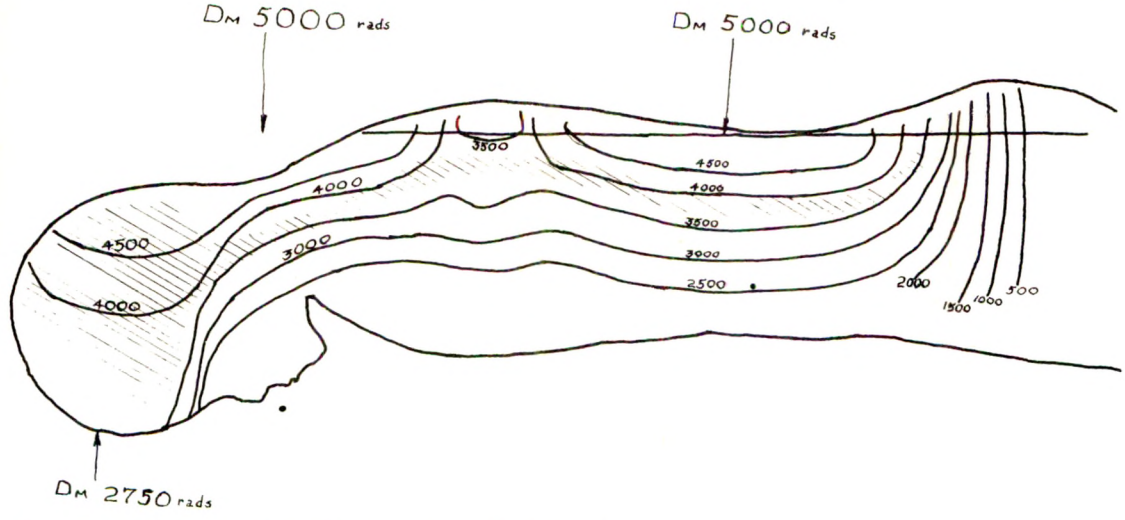

FIG. 2. Typical isodose distribution using cobalt 60, 120 cm. SSD, to treat the total cerebrospinal fluid (CSF) axis. An anterior field is used to achieve an adequate dose in the anterior cranial cavity.

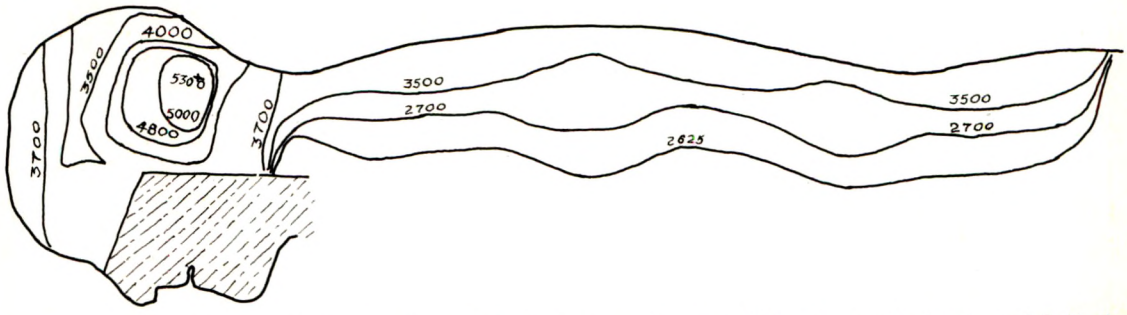

FIG. 3. Typical isodose distribution using cobalt 60 to treat the total CSF axis, employing lateral fields for the cranial contents and upper cervical spine (60 cm. SSD), and matching posterior fields for the remainder of the spine (120 cm. SSD).

had a sufficient decrease in the white blood cell counts to cause an alteration in the planned treatment. All but 4 cases showed improvement in their neurologic status to nearly normal at completion of the therapy. These 4 patients expired soon after completion of therapy.

The most common abnormal finding during the follow-up period was slow learning, although to what extent this could be attributed to the patient's neurologic problems prior to treatment could not be evaluated. In those patients treated to a depth dose of 4,000–5,000 rads to the entire spinal axis, there was noted to be some disproportionate growth in the lengths and breadths of the trunks of the survivors.

No case of induced neoplastic disease or radionecrosis of the central nervous system has been seen in the long-term survivors, although 1 patient who survived 35 months from diagnosis was found at postmortem examination to have changes compatible with a radiation necrosis; however, recurrent tumor was also present. The dose level in this 4 year old patient was 4,000 rads in 3 weeks' time to the entire cerebrospinal axis.

The most interesting portion of the material is the 3 cases, who have died of disease following a disease-free interval of more than 6 years.

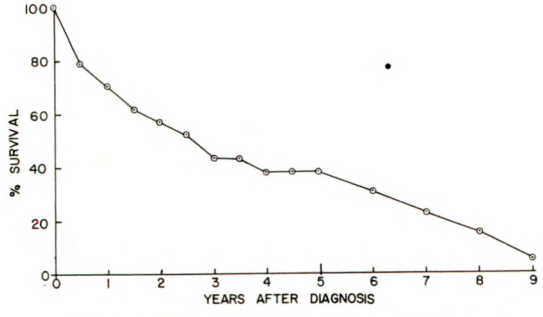

FIG. 4. Per cent surviving *vs.* years from diagnosis (Berkson-Gage).

REPORT OF CASES

CASE 1. (R.B.) This 9 year old boy presented

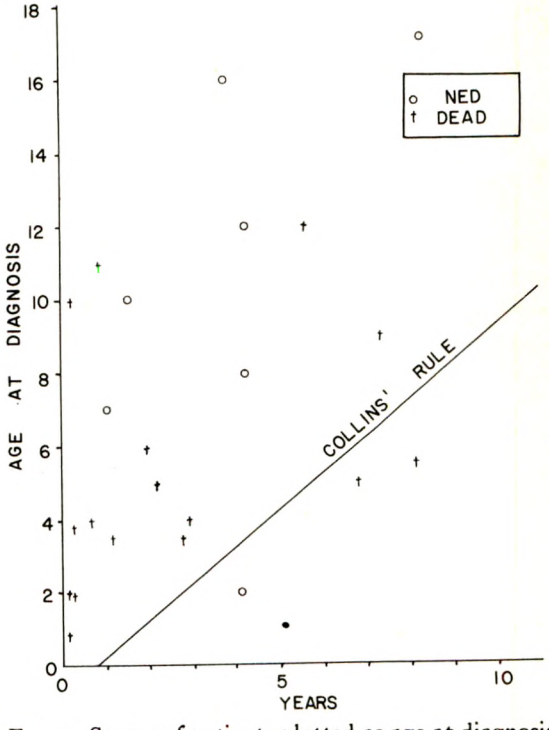

FIG. 5. Status of patients plotted as age at diagnosis *vs.* years from diagnosis. NED = no evidence of disease.

in March, 1965, with a history of 6 months of clumsiness and intermittent vomiting in the mornings and 2 months of intermittent bifrontal headaches. He was found to have papilledema, nystagmus and a right facial weakness. At the age of 2 years, the right eye was enucleated for retinoblastoma and he has had no further difficulty from this neoplasm. Skull roentgenograms demonstrated separation of the sutures from increased intracranial pressure. A ventriculogram demonstrated a large mass in the floor and anterior portion of the fourth ventricle with enlargement of all the proximal ventricles. A posterior fossa craniotomy was carried out. Tumor was found fixed to the floor of the fourth ventricle, infiltrating the obex and fixed to the cerebellar hemispheres. Two small nodules were found on the surface of the vermis. Several cubic centimeters of tumor were removed as well as the suspected seedings. Pathologic review showed that the primary tumor mass was a classical medulloblastoma. No neoplastic cells were found in the lesions described clinically as seedings.

The entire cerebrospinal fluid space was treated with a cobalt 60 unit to 5,000 rads at maximum build-up (D_m) in 32 days, using the technique shown in Figure 2, and therapy was completed without incident other than a transient decrease in his white blood cell count. He did well for 6 years without any evidence of change in neurologic status until May, 1972, when he was admitted for progressive headaches, clumsiness and blurred vision. Ventriculography and brain scanning demonstrated a mass in the posterior fossa. Exploration revealed a tumor which was interpreted pathologically as a medulloblastoma. He developed multiple problems postoperatively and had a continued downhill course, expiring approximately 2 months after operation.

Postmortem examination confirmed the recurrent medulloblastoma in the left cerebellum and floor of the fourth ventricle with invasion of the optic tract. No other sites of tumor were demonstrated.

CASE II. (S.P.) This 5 year old girl presented with occipital headaches, morning vomiting and staggering gait. She was found to have an irritable personality and papilledema. Skull findings showed "sprung" sutures and questionable enlargement of the sella with erosion. Ventriculography demonstrated great dilatation of the lateral third ventricle and the proximal portion of the fourth ventricle. The fourth ventricle was displaced superiorly and was found to have an intraventricular mass arising primarily from the left inferior portion. At posterior fossa craniotomy a large amount of tumor was found in the midline covered by a shell of a cerebellum. The firm, fleshy, gray-purple tumor filled the floor of the fourth ventricle and was moderately vascular. Decompression was accomplished. Pathologic examination showed the classical appearance of medulloblastoma. She was started on cobalt 60 teletherapy to the entire cerebrospinal fluid space using posterior fields for the spine and cranial contents and an anterior supplemental field to the head. After 2,000 rads, the spinal fields were discontinued because of a drop in the white blood cell count to 1,600. The cranial irradiation continued. By the time of completion of the cranial irradiation, the counts had returned towards normal, and after a brief rest, irradiation to the spinal axis was restarted and treated to the planned dosage. The final dose received was 5,000 rads in 28 fractions over 47 calendar days to the cranial contents and 5,000 rads D_m in 25 fractions over an 80 day period with 2,000 rads in 10 fractions over 19 days, then 3,000 rads in 15 fractions over 19 days to the spinal axis.

She did well with no evidence of disease activity until 6 years, 6 months after diagnosis when she presented with signs and symptoms of a posterior fossa mass and pain in the back. A ventriculogram demonstrated a posterior fossa mass—findings compatible with recurrence of medulloblastoma. No histologic proof of recurrence was obtained. Because of the extent of the disease, further radiotherapy was not considered advisable. She was treated with BCNU and a shunting procedure but continued to regress, expiring 5 months after recurrence of symptoms. A postmortem examination could not be obtained.

CASE III. (R.D.) This $5\frac{1}{2}$ year old girl presented with a history of intermittent early morning vomiting which became progressively more severe and more frequent over a 6 month period. Examination revealed nystagmus on upward and lateral gaze and skull roentgenograms showed "sprung" sutures. A ventriculogram was obtained which demonstrated dilatation of the lateral and third ventricles and the proximal portion of the fourth. There appeared to be a mass projecting into the fourth ven-

tricle. A posterior fossa craniectomy was carried out demonstrating a purplish tumor lying in the lower part of the fourth ventricle. There was gross total tumor removal. A pathologic diagnosis of medulloblastoma was returned. She was started on cobalt 60 radiotherapy to the entire cerebrospinal fluid axis using anteroposterior fields to the cranial contents and posterior fields to the spine. After achieving an accumulated dose level of 1,300 rads in 8 fractions, therapy to the spine was discontinued because of a white blood cell count decrease to 1,300. Treatment to the cranial area continued until completion at 5,000 rads. Although it had been planned to treat the spinal fluid axis to 5,000 rads when the blood cell counts returned to normal, this was not accomplished for reasons which could not be determined. At the completion of therapy, she had minimal symptoms and findings. She did well except for some slowness in school, and had no evidence of disease during the long follow-up period.

Frontal headaches and dizziness developed 7 years, 9 months following diagnosis. Examination disclosed nystagmus with mild papilledema. Extensive evaluation revealed a tumor mass in the right mid-parietal region with no evidence of disease in the posterior fossa. There was no clinical evidence of spinal cord seeding. A craniotomy was carried out with biopsy of the tumor mass and a diagnosis of metastatic medulloblastoma was returned. A palliative course of radiotherapy was undertaken to the area of the recurrence, delivering a depth dose of 3,000 rads in 15 sessions over 3 weeks using the cobalt 60 apparatus. There was only a minimal change in the patient's symptoms and findings and she was continued on weekly Vincristine therapy. She developed progressive neurologic findings and attempts at discontinuing or lowering the dosage of Decadron resulted in exacerbation of symptoms. Death occurred 4 months following diagnosis of the recurrence. Permission for postmortem examination could not be obtained.

DISCUSSION

During the past 25 years, the approximate 40 per cent, 5 year survival rate with modern radiotherapy treatment programs has led radiotherapists to believe that these survivors have been cured. Our neurosurgical colleagues continue to maintain that medulloblastoma is ultimately fatal and that irradiation yields only a variable prolonged remission. Our 3 cases of recurrence after 6 years, 6 years 7 months and 7 years 4 months, demonstrate that this is at least sometimes true. Only 2 of these patients had clinically proven recurrence, although the symptoms and findings in the third were such as to make the diagnosis clinically certain even though no histologic verification was obtained. Using reasoning analogous to that which has been applied by Collins[5] for nephroblastoma, one would expect, in children at least, that if there is no recurrence by the time the child has survived a period equal to his age at diagnosis plus the 9 months of gestation, one could consider him cured. Bloom[3] states that he was aware of no exception to this rule. Two of our cases, ages 5 and $5\frac{1}{2}$ at the time of diagnosis, survived with no evidence of disease activity for 6 years 7 months and 7 years 9 months following diagnosis, only to then succumb of recurrent disease. The application of Collins' rule to medulloblastoma would have to be questioned in light of our present experience.

It is of interest that even though the therapy to the spinal fields in 2 of the cases had to be interrupted because of blood cell count difficulties, the patient who received the lesser total dose to the spinal portion of the CSF axis had no evidence of seeding along this route at her demise. It is of further interest that in this patient the evidence of recurrence was in the portion of the cranial contents rostral to the tentorium and that there was no tumor at any other site, even though the area rostral to the tentorium had received essentially the same dose at the posterior fossa.

In our limited series, there appears to be no discernible difference in response among the histologic variants of medulloblastoma.[4]

It was our impression that the patients receiving extensive removal of tumor did somewhat better initially than those having

only biopsies, but there was no statistical difference in survival.

We have no explanation for the difference between our male: female ratio of 1 as compared to the more usual approximately 2:1 ratio.

SUMMARY

The authors present 3 cases of recurrence of medulloblastoma at 6 years, 6 years 7 months, and 7 years 4 months disease-free intervals from the time of diagnosis.

Two of these cases have violated Collins' rule of survivorship; *i.e.*, an interval longer than the patient's age plus 9 months being equivalent to cure.

Two of the cases were biopsy proven recurrences of medulloblastoma and in the third, the recurrence was diagnosed on the basis of clinical and roentgenographic data.

Other than for these late recurrences, our series is similar to other series reported in the literature.

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METASTATIC DISEASE OF THE SELLA TURCICA*

By M. KISTLER, M.D., *and* HENRY W. PRIBRAM, M.D., F.R.C.P.(C)
LONG BEACH, TORRANCE, AND IRVINE, CALIFORNIA

METASTATIC disease of the sella turcica has received little attention in the literature.

We wish to report the clinical and roentgenologic findings in 11 cases. Plain film roentgenograms, the appearances at angiography, encephalography and orbital venography will be described. We found a spectrum of changes that includes enlargement of the sella without evidence of destruction, sclerosis of the sphenoid bone, as well as destruction of the sella turcica and clivus. One case was diagnosed as a pituitary tumor, while another initially was thought to be a meningioma. In 2 patients there was no prior knowledge of malignancy. Four patients underwent angiography and in 3 striking abnormalities were demonstrated. Two patients had air studies, and orbital venography was performed in 1 patient.

REPORT OF CASES

CASE 1. A.M., a 50 year old male, was admitted to the hospital with a history of increasingly severe headaches of 2 to 3 months' duration. Physical examination revealed diplopia and paralysis of the left third nerve. Skull roentgenograms showed enlargement and demineralization of the sella thought to be due to a pituitary tumor, probably chromophobe adenoma. A left carotid arteriogram showed narrowing of the supracavernous internal carotid artery and some supply from the meningohypophyseal trunk without evidence of mass or abnormal vascularity. An air encephalogram (Fig. 1) revealed a mass arising from the sella with suprasellar extension and obliteration of the recesses of the anterior end of the third ventricle. Chest roentgenogram taken at this time was normal. At surgery a suprasellar mass was found which, on histologic examination, was considered to be anaplastic carcinoma.

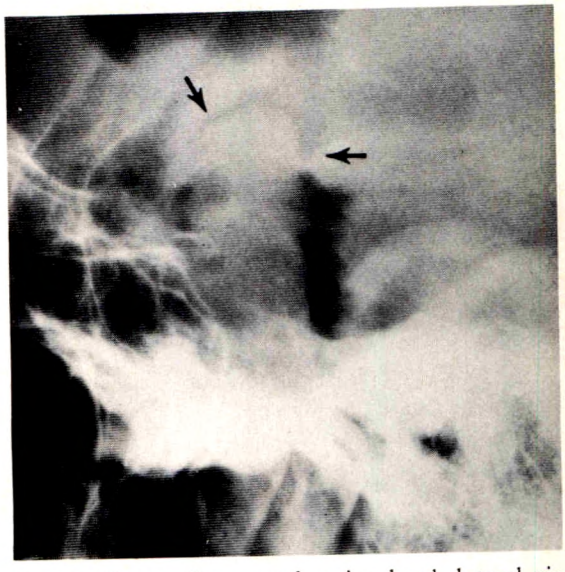

FIG. 1. Case 1. Brow-up, hanging head, lateral air encephalogram showing intrasellar mass with suprasellar extension and deformity of the anterior end of the third ventricle. The appearances are classical of a chromophobe adenoma with suprasellar extension, but surgery showed anaplastic carcinoma.

The patient expired 2 months later and autopsy showed an anaplastic carcinoma involving the right lobe bronchus with metastasis to the brain, pituitary fossa and hypothalamus.

Comment. This was the first case of metastatic disease of the sella turcica that we encountered. Prior to surgery, no suspicion was entertained that the tumor was anything other than a pituitary tumor. Even retrospective analysis of the chest roentgenogram showed no abnormality. It is likely that this was a case of metastasis to the pituitary gland itself rather than to the sphenoid bone. This would explain the fact that there was evidence of sella enlargement rather than destruction. Third nerve palsy is an unusual finding in pituitary tumors other than cases of pituitary apoplexy and might raise suspicions of metastatic disease.

* Presented at the Seventy-fifth Annual Meeting of the American Roentgen Ray Society, San Francisco, California, September 24–27, 1974.

From the Departments of Radiology, Long Beach Veterans Administration Hospital, Long Beach, California, Harbor General Hospital, Torrance, California, and the University of California, Irvine, California.

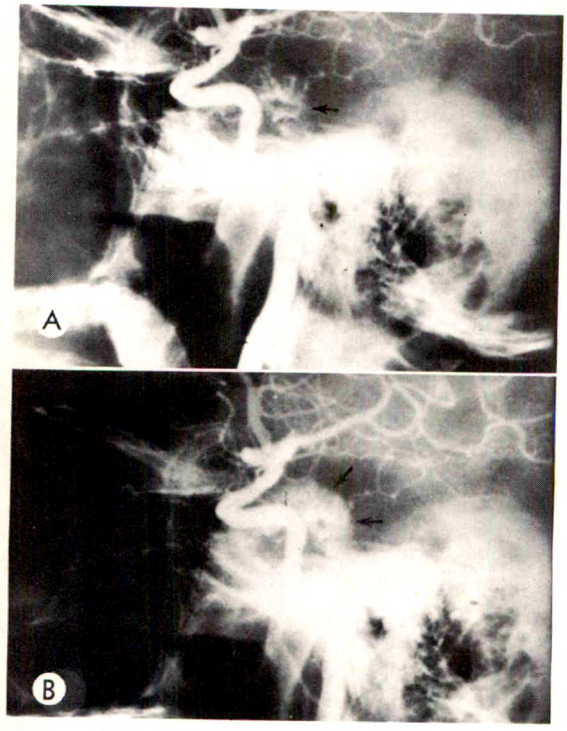

FIG. 2. Case II. (*A*) Internal carotid arteriogram showing tumor vessels derived from the meningohypophyseal trunk. (*B*) Internal carotid arteriogram showing diffuse tumor stain. The pathologic diagnosis was metastatic thyroid carcinoma.

CASE II. E.S., a 69 year old female, was admitted with a 2 week history of drooping of the left eyelid and blurred vision on the left. Physical examination showed a left third nerve palsy with ptosis. The plain skull roentgenograms showed destruction of the sella and clivus. A carotid arteriogram showed lateral displacement of the cavernous portion of the left internal carotid artery as well as a network of tortuous vessels arising from the meningohypophyseal trunk (Fig. 2, *A* and *B*). Persistent diffuse tumor stain and evidence of a large soft tissue mass were demonstrated. The initial impression was that this was a large parasellar meningioma. However, when it was learned that the patient had a history of follicular cell thyroid carcinoma treated with I^{131}, 9 years previously, a slight diagnostic adjustment was made and the tumor considered to be a thyroid metastasis. An air encephalogram demonstrated a soft tissue mass extending above the sella and lateral to the sella. At left frontotemporal craniotomy a large pulsating mass related to the internal carotid artery was noted and thought by the surgeon to be a nonresectable giant aneurysm. The surgical/radiologic controversy was resolved approximately 1 year later, when autopsy showed a large, 2×3 cm. mass extending from the floor of the sella and eroding the clivus. Lateral and superior extension was present with displacement and stretching of the left third nerve and bulging of the diaphragma sellae. Histology showed an adenocarcinoma considered to be metastatic from the thyroid.

Comment. Roentgenologically the patient initially was thought to have a parasellar meningioma. It was only after previous history of thyroid carcinoma was obtained that it was thought more likely that the sella changes were due to metastatic disease. Thyroid metastases are known to be very vascular at angiography. We have previously commented that once a sella is destroyed, it is difficult to say what caused the destruction. Large pituitary tumors may cause destruction of the sella and clivus. In patients presenting with intrasellar masses in whom a previous history of malignancy can be obtained, the possibility of metastatic disease should be entertained. The presence of the third nerve palsy reinforces this consideration. It is interesting to note that the operating surgeon was not able to recognize the true nature of the mass.

CASE III. M.S., a 71 year old female, was admitted to the hospital with a 2 week history of bitemporal headaches. Roentgenologic examination showed destruction of the sella turcica and clivus as well as a soft tissue mass extending into the right sphenoid sinus. Lumbar puncture, electroencephalogram and brain scan were normal. The patient had had a left simple mastectomy with a diagnosis of infiltrating duct carcinoma 2 years before admission. A right internal carotid arteriogram showed lateral displacement of the cavernous portion of the internal carotid artery as well as a large vascular mass supplied by vessels of the meningohypophyseal trunk (Fig. 3, *A* and *B*). The irregularity of the vessels as well as the destruction of the sella, clivus and base of skull made the diagnosis of metastatic disease the most probable.

Comment. In this instance, the diagnosis of metastatic disease was clear cut. Previous roentgenograms had shown a normal sella turcica, whereas current roentgenograms

showed evidence of massive destruction. A relatively brief history of onset, multiple cranial nerve palsies and a past history of malignancy indicated probable metastatic disease.

Case iv. D.B., a 45 year old male, was admitted with a 2 month history of left frontal headaches. Physical examination revealed ptosis of the left eyelid and a dilated nonreactive pupil with obliterated disk margin. The vision of the left eye deteriorated rapidly over the next few days. The vision on the right side was normal. A diagnosis of lymphosarcoma was made in 1969 and he was treated with both irradiation and chemotherapy in 1971.

Lumbar puncture was normal, chest roentgenograms showed osteolytic rib lesions. Skull roentgenograms revealed destruction of the sella, clivus, as well as the greater wing and lesser wing of the sphenoid on the left. Tomograms showed a soft tissue mass in the sphenoid sinus (Fig. 4, *A–D*). An orbital venogram showed non-filling of the ophthalmic veins on the left. Additional roentgen procedures were declined at this time.

Comment. The known history of malignant disease, the relatively rapid onset of multiple cranial nerve involvement together with diffuse destructive involvement of the base of the skull and simultaneous demonstration of lytic lesions in other parts of the skeleton made metastatic disease the most probable diagnosis in this case.

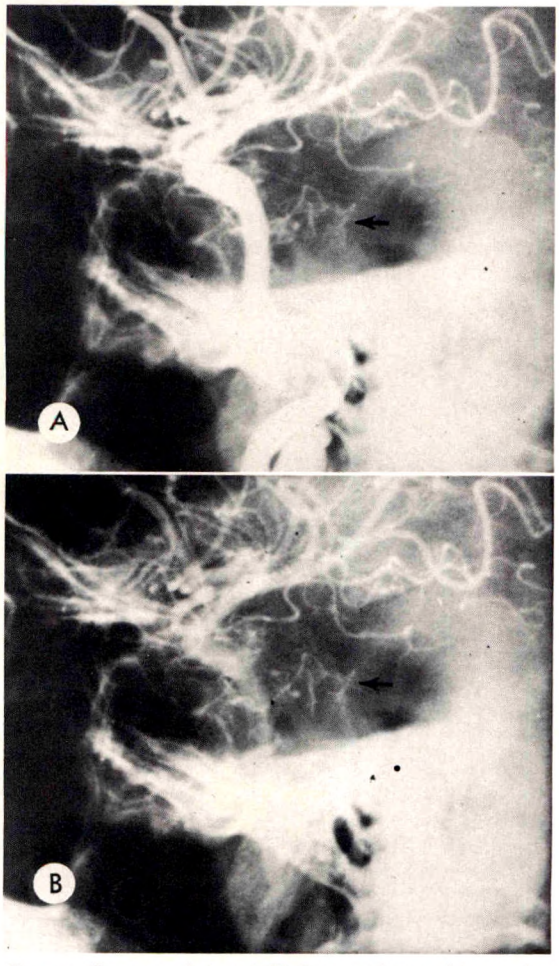

Fig. 3. Case iii. (*A* and *B*) Internal carotid arteriograms showing irregular tumor vessels derived from the meningohypophyseal trunk. Metastatic carcinoma of breast.

Case v. J.J., a 71 year old male, was admitted to the hospital with severe recurrent headaches and deteriorating physical condition. Skull roentgenograms showed lytic destruction of the floor of the sella and clivus (Fig. 5). A tumor mass was also evident in the right lung field on chest roentgenography. The patient subsequently developed multiple diffuse osteoblastic metastases and expired a short time thereafter. Autopsy revealed carcinoma of the prostate.

Comment. This is 1 of 5 cases of known prostatic metastases. It is interesting that in this case the cranial lesion was the first evidence of bone involvement, the remainder of the initial skeletal survey being normal. Only subsequently did the patient develop diffuse skeletal osteoblastic lesions. It is also noteworthy that the changes at the base of the skull were primarily lytic, and did not show the sclerotic blastic appearance found in the other 4 cases.

Case vi. N.M., a 76 year old male was admitted with a 3 month history of deteriorating mental status. Neurologic examination revealed no localizing abnormalities. Skull roentgenograms showed thickening and sclerosis of the planum with destruction of the clivus, sella and extension into the sphenoid sinuses (Fig. 6). A bone survey was normal. A brain scan was obtained and demonstrated abnormal uptake in the anterior right parasagittal region. A subsequent carotid angiogram showed pathologic vessels arising from the meningohypophyseal trunk as well as from the artery to the inferior cavernous sinus.

The patient expired during this admission. At autopsy metastatic carcinoma of the pros-

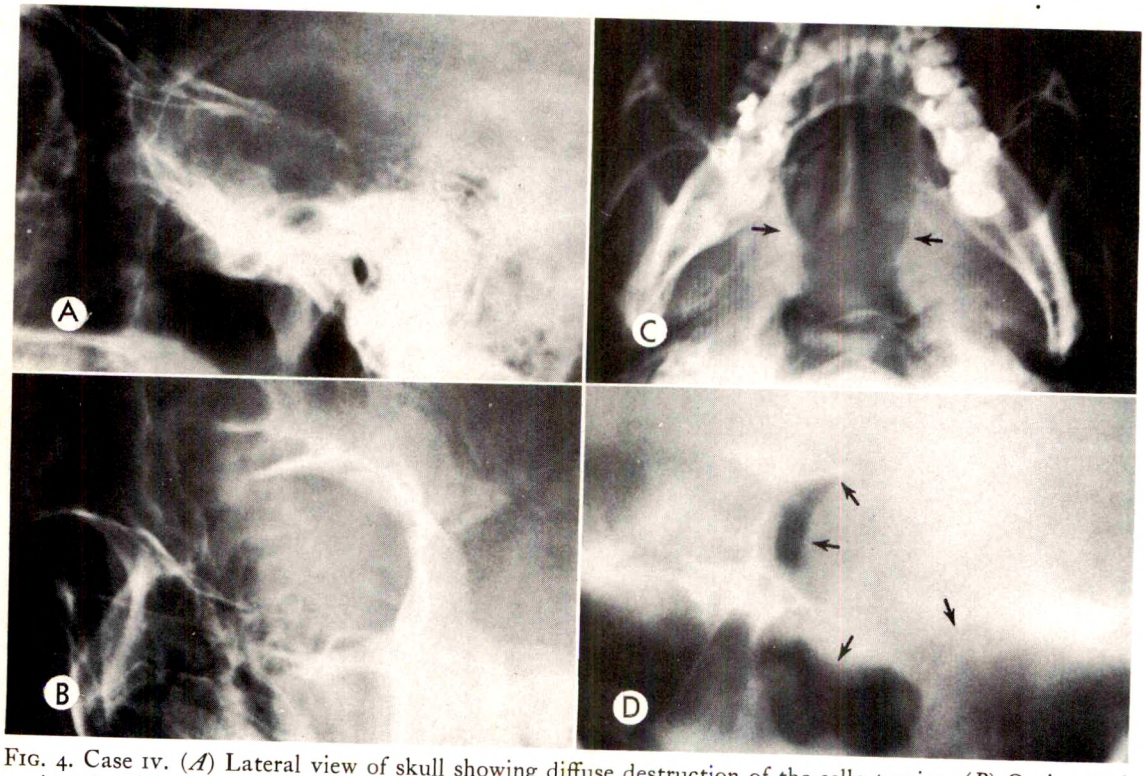

FIG. 4. Case IV. (*A*) Lateral view of skull showing diffuse destruction of the sella turcica. (*B*) Optic canal view showing destruction of the posterior wall of the orbit. (*C*) Base view showing destruction of base of skull. (*D*) Anteroposterior tomogram of the sphenoid showing soft tissue mass of lymphosarcoma.

tate involving the floor of the skull with extension into the base of the brain was demonstrated. In addition, a reddish brown ill defined tumor mass was noted within the sella which, on histologic examination, proved to be a chromophobe adenoma. The destruction of the sella was erroneously attributed to carcinoma of the prostate.

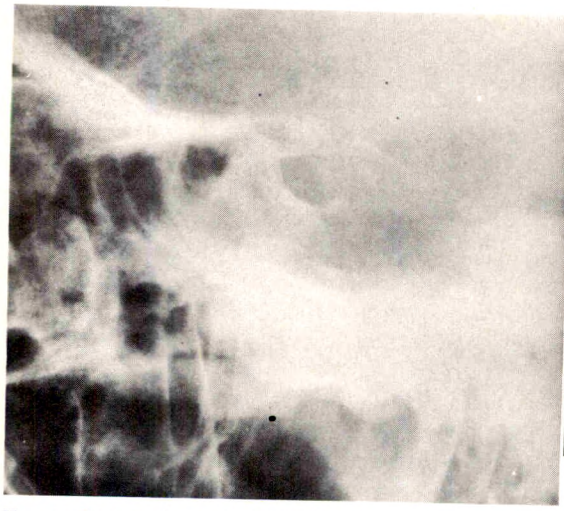

FIG. 5. Case V. Lateral view of skull showing destruction of the posterior floor of the sella turcica as well as the clivus due to prostatic carcinoma.

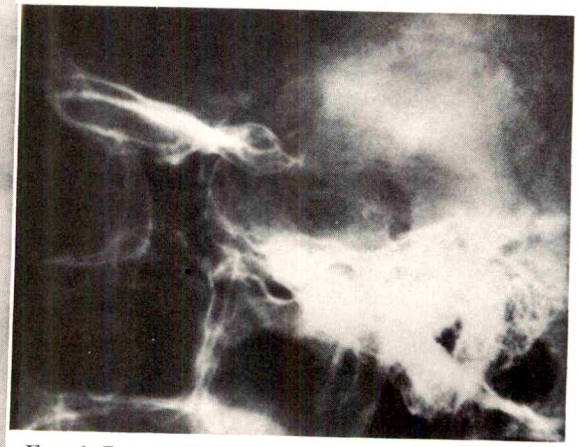

FIG. 6. Case VI. Lateral roentgenogram of skull showing enlargement and destruction of the sella turcica as well as thickening of the planum due to prostatic carcinoma as well as a chromophobe adenoma.

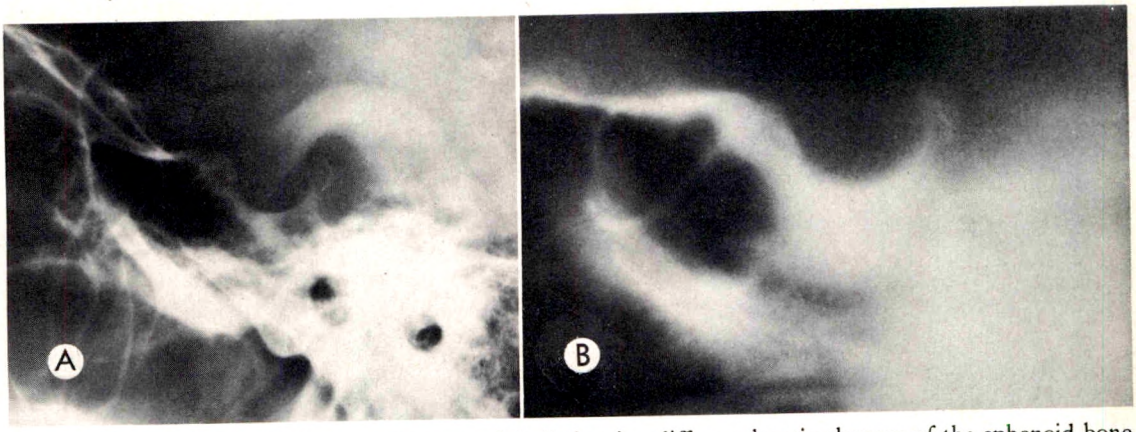

Fig. 7. Case vii. (*A*) Lateral roentgenogram of skull showing diffuse sclerotic changes of the sphenoid bone and floor of the sella turcica due to prostatic carcinoma. (*B*) Lateral tomogram showing diffuse osteosclerotic changes in the sphenoid bone due to prostatic carcinoma.

Case vii. T.H., an 82 year old male, had known adenocarcinoma of the prostate and multiple osteoblastic metastases. Admitting neurologic examination revealed no abnormalities. Skull roentgenograms demonstrated marked sclerosis of the floor of the sella, involving the clivus and extending into the sphenoid sinus (Fig. 7, *A* and *B*).

Case viii. C.L., a 59 year old white male, had been admitted with a diagnosis of prostatic carcinoma 2 years previously and subsequently developed diffuse osteoblastic bone metastases. Neurologic examination revealed no abnormalities. Skull roentgenograms showed sclerotic thickening of the floor of the sella and clivus (Fig. 8). Skull roentgenograms 3 years previously were normal.

Case ix. M.B., a 52 year old male, was admitted with known metastatic disease secondary to carcinoma of the prostate. Lateral skull roentgenograms showed marked sclerosis of the floor of the anterior and middle fossae with extension posteriorly to the floor of the sella and posterior portion of the sphenoid sinus (Fig. 9). Skull roentgenograms 2 years previously were normal.

Case x. R.R., a 60 year old male, developed loss of vision in the left eye. He was known to have carcinoma of the prostate with metastases. Skull tomography showed sclerosis of the floor of the sella, dorsum, clivus and the anterior clinoid processes (Fig. 10).

Comment. Cases vii, viii, ix and x. These 4 cases are characterized by a relatively wide age range, 52 to 82 years, and no localizing neurologic abnormality, with the common denominator of the skull roentgenographic findings being a diffuse osteoblastic involvement of the base of the skull. Three of the 4 cases had demonstrable osteoblastic lesions in the remainder of the skeleton at the time of the abnormal skull roentgenograms. We were surprised at the high

Fig. 8. Case viii. Lateral tomogram of sphenoid bone showing diffuse sclerotic changes of the dorsum sellae and clivus due to prostatic carcinoma.

FIG. 9. Case IX. Lateral roentgenogram of skull showing marked expansion and sclerotic changes in the orbital roof as well as sclerotic changes in the sphenoid bone and the floor of the sella turcica due to prostatic carcinoma.

incidence of metastatic disease due to carcinoma of the prostate, as we had previously considered this to be a rarity. In part, this may be the reflection of the patient population, as most of the cases came from the Veterans Administration Hospital.

CASE XI. H.J., a 48 year old female, had a previous history of breast carcinoma with multiple osteolytic bone metastases on skeletal survey. The neurologic examination was normal. Plain skull roentgenograms showed mixed osteolytic and blastic involvement of the sella and clivus (Fig. 11).

DISCUSSION

Eleven cases of proven metastatic disease of the sella turcica are reported (Table 1). The range of roentgenographic findings is quite broad and any discussion of the differential diagnosis would include fibrous dysplasia, meningioma *en plaque*, nasopharyngeal carcinoma, craniopharyngioma, chordoma, glioma and pituitary adenoma. We are of the opinion, however, that in any one case there is the possibility that the findings will at least suggest the correct diagnosis.

The most helpful differentiating points are a known history of malignant disease and positive skeletal surveys. Nine of our cases had known malignant disease and 7 of these had positive skeletal surveys. However, in 2 the history of malignant disease was quite remote (9 years and 3 years), 3 cases had normal skeletal surveys at the time of the first sellar changes, and 2 cases had no known history of cancer. It is also

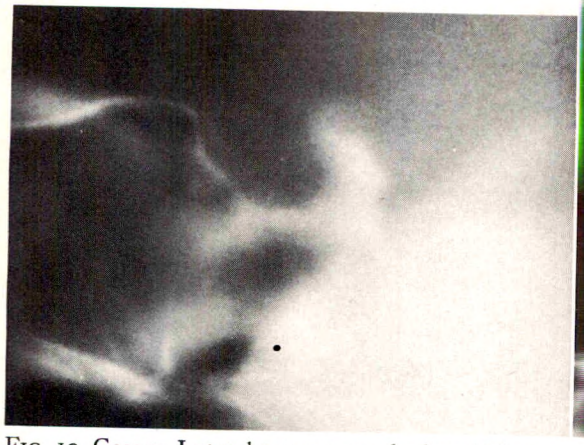

FIG. 10. Case X. Lateral tomogram of sphenoid bone showing sclerotic changes due to prostatic carcinoma.

FIG. 11. Case XI. Lateral roentgenogram of skull showing marked sclerotic and lytic changes due to metastatic carcinoma of the breast.

TABLE I

SUMMARY OF CASES

Case	Age and Sex	Clinical Presentation	Skull Roentgenograms	Skeletal Survey	Angiographic Study	PEG	Diagnosis
I.	50 M AM	3 mo. history of headaches with diplopia of 3 weeks' duration; left III palsy and papilledema; no known history of prior malignant disease	Sellar enlargement	Normal	Nonspecific narrowing of supracavernous portion of left carotid; no mass effect or abnormal vascularity	Mass with suprasellar extension	Bronchogenic carcinoma (autopsy proven)
II.	69 F ES	2 wk. history of left III palsy, carcinoma of thyroid 9 yr. previously	Sellar destruction	Normal	Vascular mass	Mass with suprasellar extension	Carcinoma of thyroid (autopsy proven)
III.	71 F MS	2 wk. history of diplopia and headache carcinoma of breast, for 2 yr.	Destruction of sella with soft tissue mass	Lytic lesion of spine	Vascular mass	—	Carcinoma of breast
IV.	45 M DB	2 mo. history of left frontal headaches; left III nerve palsy; known metastatic lymphosarcoma	Destruction of the sella, clivus and greater wing of sphenoid	Metastatic lesions	Abnormal orbital venogram	—	Lymphosarcoma
V.	71 M JJ	1 yr. history of headaches and diplopia; no known history of prior malignant disease	Lytic destruction of posterior floor of sella and proximal clivus with soft tissue mass	First study normal; later multiple osteoblastic lesions	—	—	Prostatic carcinoma (autopsy proven)
VI.	76 M NM	deteriorating mental status; known cancer of the prostate	Thickening and sclerosis of the planum with sellar destruction	Normal	Vascular mass (abnormal brain scan)	—	Prostatic carcinoma (autopsy proven). Chromophobe adenoma
VII.	82 M TH	deteriorating mental status; known metastatic disease of the prostate	Sclerotic destruction of floor of sella	Metastatic lesions	—	—	Prostatic carcinoma
VIII.	59 M CS	therapy for cancer of prostate 2 yr. previously	Sclerotic destruction of floor of sella	Normal skull roentgenograms 3 years previously. Metastatic lesions	—	—	Prostatic carcinoma
IX.	52 M MB	known metastatic disease of prostate; painful exophthalmos of right eye of 6 months' duration	Hyperostosis of floor of middle and anterior fossa and floor of sella	Metastatic lesions; normal skull roentgenograms 2 years previously	—	—	Prostatic carcinoma
X.	60 M RR	known metastatic carcinoma of prostate	Sclerosis of sella turcica and anterior clinoid processes	Metastatic lesions	—	—	Prostatic carcinoma
XI.	48 F HJ	known metastatic breast cancer	Lytic and blastic involvement of sella	Metastatic lesions	—	—	Carcinoma of breast

possible that the first evidence of bone metastasis may be on the skull roentgenogram. Skeletal survey is then pursued only if the examiner thinks of the possibility of metastatic disease. This was certainly the situation in Case V.

Seven of our cases presented with visual complaints; 2 with third nerve palsy alone; 1 with diplopia and third nerve palsy combined; 2 with diplopia; 1 with exophthalmos; and 1 with loss of vision. It is interesting to note that in a prior report it was felt that third nerve palsy was quite rare.[3] We consider that a third nerve palsy, other than in cases of pituitary apoplexy, should raise suspicion of metastatic disease.

The plain film skull roentgenogram may also lead the examiner to the correct diag-

nosis. The similarity between fibrous dysplasia, meningioma *en plaque* and prostatic metastases to the base of the skull has been discussed in the past.[5,8,9,12–14] Kirkwood *et al.*[8] and Shapiro and Janzen[14] mention the differentiating point that meningioma *en plaque* involves only the bone contiguous with the dura and, therefore, does not cause sclerosis of other portions of the skull. In 6 of 8 patients with exophthalmos and sclerosis of the base of the skull secondary to metastatic disease of the prostate reported by Kirkwood *et al.*,[8] sclerosis of the zygomatic bone forming the lateral wall of the orbit was also noted.

Most patients with fibrous dysplasia present with complaints of progressive facial asymmetry and deformity. However, the most common neurologic complaints are visual loss and impairment of hearing. Sassin and Rosenberg[12] found visual loss in 8 of 10 patients who had bone involvement around the optic canal and make the point that the latter finding was seen only in patients having both frontal and sphenoid bone involvement.

We are of the opinion that the nature of the sclerosis itself allows one to favor the correct diagnosis. In our cases the sclerosis secondary to prostatic metastases was much more dense and homogeneous than that seen with either fibrous dysplasia or meningioma.

Sclerosis of the base of the skull, secondary to nasopharyngeal carcinoma, has been reported in the past. Belanger and Dyke[2] reported 2 cases with sclerosis of the dorsum sellae and body of the sphenoid and basiocciput. Epstein[4] reported 2 cases of nasopharyngeal carcinoma with plain film roentgenographic findings of sclerosis. Potter[10] reported 2 additional cases demonstrating a combination of destruction and sclerosis of the base of the skull as well as sclerosis of the odontoid and anterior arch of the atlas. The most common presentation,[6] however, is destruction of the base of the skull with an associated soft tissue mass in the nasopharynx. In these cases, the correct diagnosis would present little problem.

The angiographic findings may also allow one to make the correct diagnosis. In 3 of the 4 cases studied by carotid angiography, a vascular mass was demonstrated. Baker[1] in a recent series demonstrated prominent tumor vascularity in only 8 of 21 parasellar meningiomas, 19 of 56 cases of pituitary adenoma, in 1 of 19 cases of craniopharyngioma and no vascularity in 2 mucoceles. He also states that the vascular blush seen with meningioma is less intense than that seen with most metastases.

Even in retrospect, the blush evident in our Case 11 would be difficult to distinguish on this basis. We are of the opinion that perhaps the nature of the vascularity is more helpful. The vessels associated with a meningioma are much more regular, without the bizarre characteristics seen in our cases. As more cases are studied with this point in mind, it will be interesting to see if this is a valid differential point.

SUMMARY

Eleven cases of known metastatic disease to the sella turcica are reported.

The clinical, plain film roentgenographic and angiographic presentations are discussed with reference to the differential diagnosis and possible distinguishing characteristics of metastatic disease.

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We wish to thank Dr. D. Torrance, Clinical Professor of Radiology of the University of California, Los Angeles, and Chief of Radiology at Bay Harbor Hospital, Torrance, for permission to include Case v.

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ANGIOGRAPHY OF CEREBELLAR HEMORRHAGE SECONDARY TO HYPERTENSION*

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CEREBELLAR hemorrhage is an extremely critical lesion and is usually treated as a surgical emergency.[3,7] Neurologists and neurosurgeons have become increasingly aware of the entity, with recent reports indicating more success in making the diagnosis clinically.[2–4,6] Radiographic studies, particularly posterior fossa angiography, are valuable in localizing the site of the hemorrhagic mass, but have not been described in the radiographic literature.

Findings in 5 patients with cerebellar hemorrhage secondary to hypertension will be discussed.

MATERIAL

Five patients have been seen at the University of Tennessee Medical Units in 18 months with surgically proven cerebellar hemorrhage secondary to hypertension. Ages ranged from 42 to 69 years. The presenting symptoms were progressive headache, nausea, and vomiting. All were hypertensive. Stupor progressing to coma was present in 3 of the 5. Truncal ataxia was shown in 2, but could not be tested in the others. All had conjugate deviation of the eyes away from the side of the lesion. Paresis and sensory deficits were not present in any patient. These findings led to the clinical suspicion of cerebellar hemorrhage.

A posterior fossa craniectomy was performed with evacuation of an acute hemorrhagic clot from the cerebellum in each patient. Two of the patients left the hospital much improved following surgery, 1 being essentially symptom-free. One of the remaining 3 patients initially was improved, but subsequently expired from infarction of the brain stem. Two patients expired within 12 hours of admission.

RADIOGRAPHIC FINDINGS

The posterior fossa was studied prior to surgery by retrograde brachial angiography in 2 patients and by the transfemoral route in 1 (Fig. 1–3). A cerebellar mass was shown in each by such findings as contralateral displacement of the posterior inferior cerebellar artery (PICA) and its vermian branches, posterior and contralateral displacement of the inferior vermian veins and elevation of branches of the ipsilateral superior cerebellar artery.

In 1 patient, ventriculography (Fig. 1*D*) following angiography (Fig. 1, *A–C*) showed a contralateral shift of the 4th ventricle confirming the angiographic findings of a cerebellar mass. Ventriculography was the only radiographic procedure in 1 patient and showed occlusion of the midportion of the aqueduct.

Hydrocephalus was present in each patient as shown by either carotid angiography or ventriculography and was presumed to be due to partial or complete obstruction of the aqueduct secondary to displacement by the cerebellar mass. Relief of this obstruction and ventricular decompression are the major objects of immediate surgery.

The patient not studied radiologically was felt to be deteriorating too rapidly to delay posterior fossa exploration further. Clinical findings were sufficient for the diagnosis.

A sixth patient with the same symptoms as described above was seen. In contrast to the other patients, she was only 29 years old and normotensive. Preoperative an-

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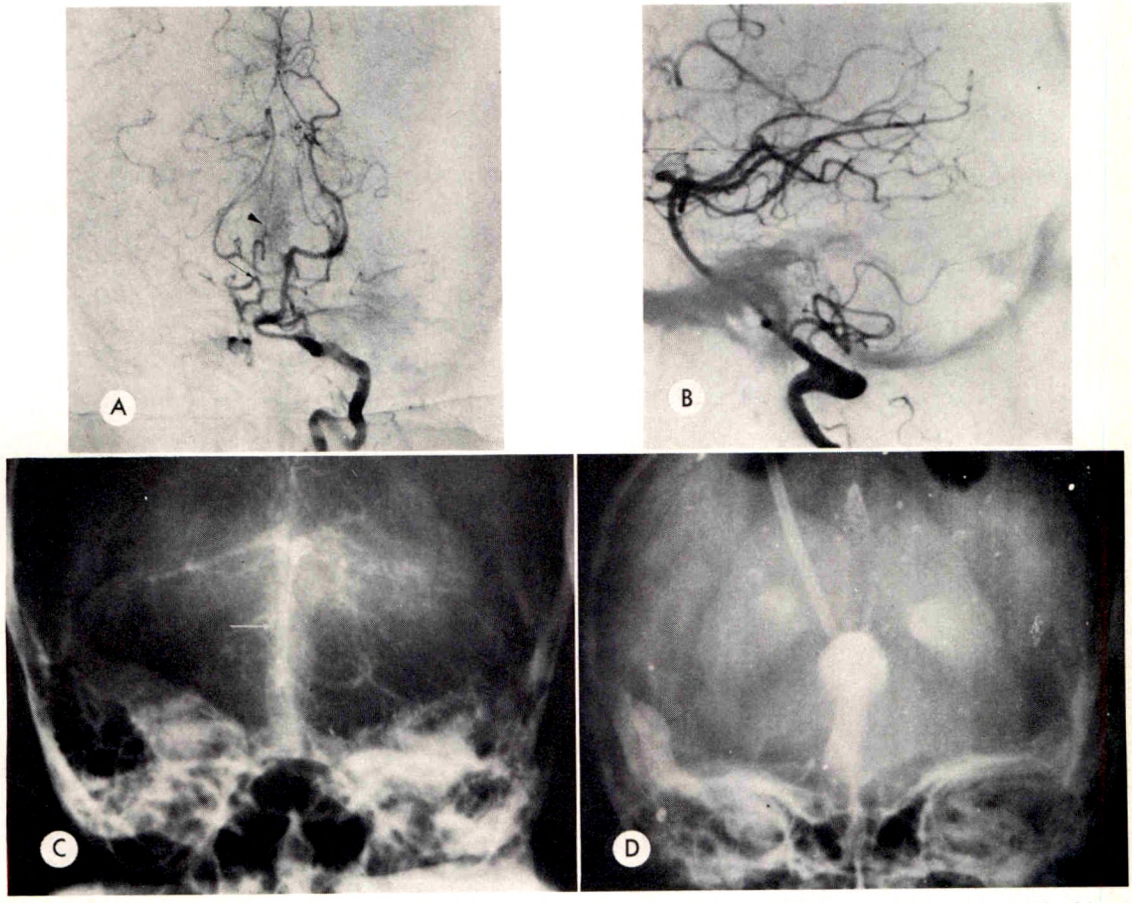

Fig. 1. A 42 year old Black woman had sudden onset of occipital headaches, dizziness and vomiting. The blood pressure was 280/130 mm. Hg. The patient was alert with conjugate deviation of the eyes to the right. Selective left vertebral angiography *via* the femoral route was performed. A hemorrhagic mass was removed from the left cerebellar hemisphere. (*A*) Anteroposterior arterial phase. Both PICAs fill. Shift of choroidal point (arrow) and inferior vermian branch (arrowhead) of right PICA from left to right. (*B*) Lateral arterial phase. Anterior displacement of basilar artery. (*C*) Anteroposterior venous phase. Displacement of inferior vermian veins (arrow) from left to right. (*D*) Conray ventriculogram. Shift of 4th ventricle from left to right with flattening of left ventricular margin.

giography was not performed because her condition was considered too precarious to delay surgery. A large clot was removed from the left cerebellar hemisphere with immediate clinical improvement. Transfemoral vertebral angiography 12 hours after surgery (Fig. 4, *A–C*) showed the source of the intracranial hemorrhage to be an arteriovenous malformation involving the medulla. No further surgical procedures are planned.

DISCUSSION

Cerebellar hemorrhage was first described by Seidillot in 1813.[1] Current reports indicate that it comprises 10 per cent of all intracranial hemorrhage.[1,2,7] Some controversy has surrounded the entity because of earlier opinions[7] that the diagnosis was not possible on clinical grounds. More recently, Fisher *et al.*[3] have described specific clinical findings and expressed confidence that a firm clinical diagnosis can be made. Dysarthria, contralateral conjugate deviation of the eyes, a decreased or absent caloric response, truncal ataxia and relative retention of motor and sensory function in the limbs have been empha-

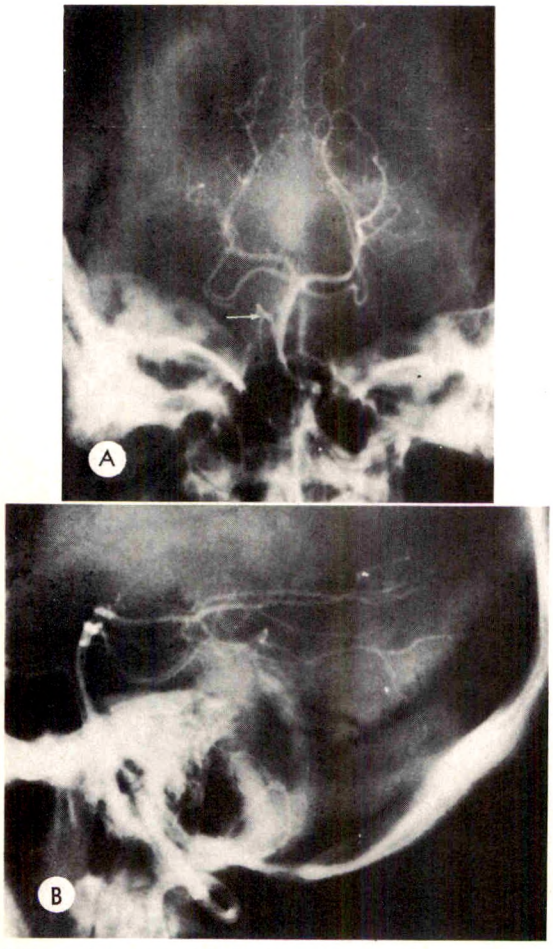

FIG. 2. A 69 year old Black man had a history of sudden onset of dizziness, inability to walk, vomiting, and truncal ataxia. The blood pressure was 210/130 mm. Hg. A left brachial angiography was performed. A hemorrhagic mass was partially removed from the left cerebellar hemisphere. (*A*) Anteroposterior arterial phase. Shift of choroidal point (arrow) of left PICA from left to right. (*B*) Lateral arterial phase. Anterior displacement of the basilar artery.

sized as extremely helpful findings.

McKissock *et al.*[7] were not able to observe any positive angiographic findings in the posterior fossa. However, subsequent authors[2,5,6,9] have reported findings of a posterior fossa mass on angiography. Ventriculography[2,6,7] has also been useful in demonstrating displacement or obstruction of the aqueduct and displacement of the fourth ventricle from the midline. Hydrocephalus has been a consistent finding. The radiographic recognition of a posterior fossa mass is of importance because the accepted treatment is immediate surgical evacuation of the cerebellar clot.[3] In fact, the neurologic status of these patients is so precarious that, in those with typical clinical findings, immediate surgery is often performed rather than waiting for radiographic confirmation of the lesion.

Several of the reports[5,8,10] in the literature deal primarily with cerebellar infarction secondary to vascular occlusion associated with adjacent edema but without hemorrhage. In contrast, our patients primarily bled into the cerebellum due to hypertension. Both primary infarction and primary hemorrhage may result in a mass effect. It appears, however, that the patients with hemorrhage deteriorate more rapidly because the mass enlarges more quickly. Primary cerebellar hemorrhage is critical because of its proximity to medullary and pontine centers plus the confining effect of the tentorium.[6]

Moscow and Margolis[9] described the angiographic findings in pontine hemorrhage secondary to hypertension and

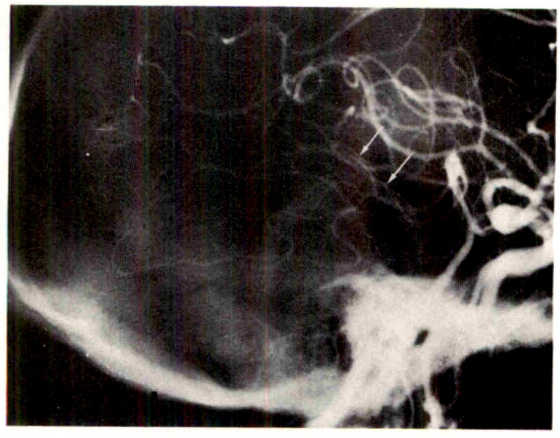

FIG. 3. A 67 year old Black man had severe headache, vomiting, and slurred speech. The blood pressure was 240/120 mm. Hg. Right brachial angiography was performed. Superior displacement and rounding of quadrigeminal portion of the superior cerebellar artery (arrows) are present. Inferior displacement of choroidal point was suspected. At surgery, a hematoma involving the right cerebellar hemisphere with extension into the pons was found.

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PRESIDENT
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THE NETWORK CONCEPT IN THE CANCER CENTER*

PRESIDENTIAL ADDRESS, 1974

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SAN FRANCISCO, CALIFORNIA

A NEWLY diagnosed cancer patient, perhaps a lumber mill employee in the small community of Eureka, California, 280 miles north of San Francisco, frequently is placed in a dilemma. Facing a lengthy stay away from home, wrenched away from his family, friends, his own physician, even losing his employment, is it any wonder that he seeks alternatives to going to the metropolitan center for optimal care? It is not unusual to encounter the cancer patient from such rural communities who has never ventured outside his own community for any reason, let alone for health reasons. This same person is terrified of the loneliness of the city. He is homesick and emotionally and economically threatened. In truth, these apprehensions often share equal place with his fears of a life threatening disease.

Isn't it time to consider alternatives to the traditional concepts that optimal cancer care can be administered only in a geographically centralized location, usually in a large metropolis? Isn't it possible that optimal cancer care could be made available to the majority of cancer patients within their own communities, within reach of home and loved ones? It is possible if we are willing to go beyond the concepts of the center surrounded by satellites and embrace the concept of a center comprised of a multitude of communities, institutions, and health professionals bound together in serving the cancer patient regardless of his community size or geographic location . . . the *Network Concept.*

Key to concepts of network and cooperation is the utilization not only of cancer specialists and facilities within a region, but the active involvement of the patient's local physician in the management of his patient. The patient's physician is then a participant in the networks' cancer activities. The Flood committee report on June 21, 1973, in a congressional report commenting on cancer control programs authorized by the National Cancer Act of 1971 stated, "the plans are impressive, but the committee (Committee on Appropriations) has not been impressed with past efforts to involve local practicing physi-

* Presented at the Fifty-sixth Annual Meeting of the American Radium Society, Maui, Hawaii, April 21–25, 1974.

cians in cancer control or, for that matter, in the cancer centers programs. The local physician is essential to the success of any national health program as it is the local practitioner who is on the medical firing line daily. It is the hometown practitioner who is the first to see the cancer patient and it is his capacity for early diagnosis and his awareness of the most effective early treatment that will determine the success of the program and its eventual benefit to people."

The American Cancer Society, from its very beginning has stressed the patients' early recognition of cancer symptoms and signs and calling these to the attention of their physicians.

The traditional concept of the cancer center as it has evolved over the decades is that of a large geographic building or buildings, usually in a large city, inhabited by cancer patients, specialists, research workers and students, and engaged in care as well as research and training. The patients are recruited from the surrounding communities, go to the center and return to their communities after treatment. The local physicians play a limited role under these circumstances.

Originally in the advent of specialized radical surgery and radiation therapy, cancer care consisted of less radical surgery and/or supportive medical care. Later as radiation therapy developed, of necessity because of skilled cancer surgeons and trained radiation therapists and because of the expense and complexity of radiation therapy instrumentation, it was a natural and beneficial consequence that the congregation of such specialists and instrumentation occurred. The benefits are easily recognizable—experience increased as the patient volume increased, staff interplay contributed to multidiscipline management of the cancer patient, maximum utilization of both staff and equipment resulted. Is it any wonder that this was considered the optimum in patient care? Nevertheless, there always remained the nagging feeling that maximum numbers of cancer patients were not able to avail themselves of these ideal cancer centers, particularly if they lived in communities remote from the center.

The British and Scandinavians developed the centralized cancer center to its highest degree and evolved satellite centers serviced by the parent center. While definitely an improvement on the isolated non-communicative center, patients were still removed from their home environments for specialized care. Radiation therapy, particularly in the European centers, became the keystone on which centralization rested. Megavoltage equipment and techniques necessitated centralized teams of radiation therapists, radiological physicists and technicians, again primarily because of economics and scarcity of skilled personnel.

In the United States such centralization developed centers of excellence, *i.e.*, M. D. Anderson Hospital, Memorial Center, Ellis Fischel, Roswell Park, Penrose Cancer, Swedish Tumor Institute and others which epitomized specialized centralized cancer care. Interestingly enough, medical schools of the United States lagged in the development of cancer centers, probably because of the departmental specialty oriented method of teaching and practice. Certainly, another important factor is the persistent failure of many medical schools even today to recognize radiation therapy as an oncological specialty distinct from diagnostic radiology.

The American Cancer Society and the National Cancer Institute, recognizing the obvious necessity for increased research and training in cancer, infused millions of dollars into programs which further strengthened the centralization philosophy.

In a purely philosophical sense, centralized cancer care may be the preferable means to providing optimal cancer care, but is it available to sufficient numbers of cancer patients in our country irrespective of economic and geographic factors?

Among the many successful Regional Medical Programs (RMP) there were few

in cancer. Again perhaps the single most important reason for failure of these programs was the persistence of medical school based centers—satellite concepts with minimal involvement of patients and physicians in smaller communities. Another reason was the artificial concept of limiting programs, physicians and institutions to within specific geographic boundaries. The Regional Medical Programs which most often succeeded did so because clinical care was taken into the community—not out of it.

The Cancer Centers Program of the National Cancer Institute has generated tremendous activity among the medical schools of this nation, anxious to participate in this program. The pitfalls of the RMP programs are the same pitfalls that may well cripple the centers programs if they are not avoided, namely centralization, isolation and non-recognition of the communities role and involvement in the centers program. The community must not be represented only by a sampling of associated hospitals lying within communication by a local phone call.

Among the cancer centers programs in the United States today there is to date an unfulfilled need for an alternative to the center—satellite concept of a cancer center and a need for coordinated decentralized multidiscipline cancer center. This center should not be a central geographic entity with surrounding satellites, but a multidiscipline *network* of individual cancer centers, schools and organization ranging in location from the metropolitan areas to the smaller communities. Indeed the center becomes a part of the network as well as the network being a component part and resource of the comprehensive cancer center. The development of the network with its obvious advantages is not without problems. In Northern California there are problems of patient and physician remoteness created by geographic and demographic considerations. An innovation network of physicians and the community hospitals throughout Delaware is well into its organization and planning development. The Delaware network is addressing itself to problems of delivery of current cancer care technology to physicians in a state (Delaware) which has no medical school. This network of organizations and physicians, by banding together, can better share the resources and will result in improved patient care, flow of information and reduced cost of patient care delivery. The transfer of new cancer care technology to the private physician is facilitated. Within the framework of a network operation, programs in cancer detection, diagnosis, clinical staging and tumor grading, treatment techniques, psycho-social rehabilitation, data recall, training and basic and clinical research can evolve from the community level. Perhaps as many as 90 per cent of all cancer patients could receive quality cancer care within reasonable distance from their homes, families, friends and livelihood, utilizing such a system.

Radiation oncologists can play a key role in the development of multidiscipline cancer center networks. Among the clinical oncologists they, more than any other specialty, devote their practices strictly to oncology, and thus, can serve as a focus for the other disciplines in cancer care. Despite the recognized fact that there are insufficient total numbers of radiation oncologists in the United States, as more are trained, more will settle into the smaller communities and can often unify fragmented cancer services into multidiscipline approaches to the disease of cancer. It is particularly tragic that once highly organized and productive training programs sponsored by the National Cancer Institute in radiation, medical and surgical oncology are no longer funded.

The National Cancer Institute Cancer Centers Program has provided funds for planning for the expansion of designated existing centers and the development of new specialized and comprehensive cancer centers.

Among the institutions utilizing National Cancer Institute planning funds is the

West Coast Cancer Foundation with headquarters in San Francisco. While San Francisco based, its epicenter of activities lies north of San Francisco in communities throughout Northern California. The West Coast Cancer Foundation is a non-profit organization incorporated in the State of California in December, 1971, in response to the need to develop more extensive cancer care programs in the region. Its purpose is to plan, organize and implement an innovative comprehensive multidisciplinary program in cancer research, education and clinical care in Northern California and Northwestern Nevada utilizing a network concept.

The West Coast Cancer Foundation network is so designed not to exclude anyone potentially interested in participating in such a concept, nor to limit its participants' affiliations or associations with other organizations or programs. The network is a partnership of individuals, organizations and hospitals, including community lay leaders, private community physicians and clinics, cancer specialists, local American Cancer Societies, community hospitals, major San Francisco medical centers, a major dental school and a developing School of Health Professions. It is being expanded to include religious leaders, county medical societies and state and county health agencies. It is the result of relationships and mutual trust developed by members of the West Coast Cancer Foundation over the last 15 years, only now developing a formal organizational structure. Its programs are atune to a national effort to reach the cancer patient in the community, recognizing that the key to the network is the private community doctor. All cancer programs are being developed out of the network so as to include all participants in program development as well as implementation. It is vital to the success of the network that the participants feel and actually are active in the design of the network, its planning process, and ultimate implementation and operation of its programs. There are different voids in different communities in Northern California due to the differing levels of medical sophistication in each community. The network can fill these voids by applying network resources where the need exists. As a practical example of this, the West Coast Cancer Foundation provides radiation physics services to multiple institutions in the smaller communities as well as to major San Francisco bay area hospitals.

The American Radium Society, founded in 1916, in its own development as a scientific society over almost 60 years, epitomizes the evolution of cancer care in this country. The Society was founded primarily by surgeons who were utilizing ionizing radiations as well as surgery in the management of cancer. As radiation therapy struggled to become a fully recognized oncological specialty in the United States, the Society became a refuge and source of strength for the radiation oncologists. It was from the strong base provided by the American Radium Society to the radiation therapy community that the American Society of Therapeutic Radiology was given birth and has grown to its present status. The American Radium Society in recent years has stressed that its aims and goals are to further the multidiscipline concepts in the management of cancer. It is appropriate that many members of this Society are active today in the development of multidiscipline cancer centers. It is imperative that the membership of a Society such as ours, composed of cancer specialists, not forget the plight of the cancer patient in the smaller communities or the patients' physician in that same community. They are as much a part of the cancer centers as the complex of buildings in the metropolis.

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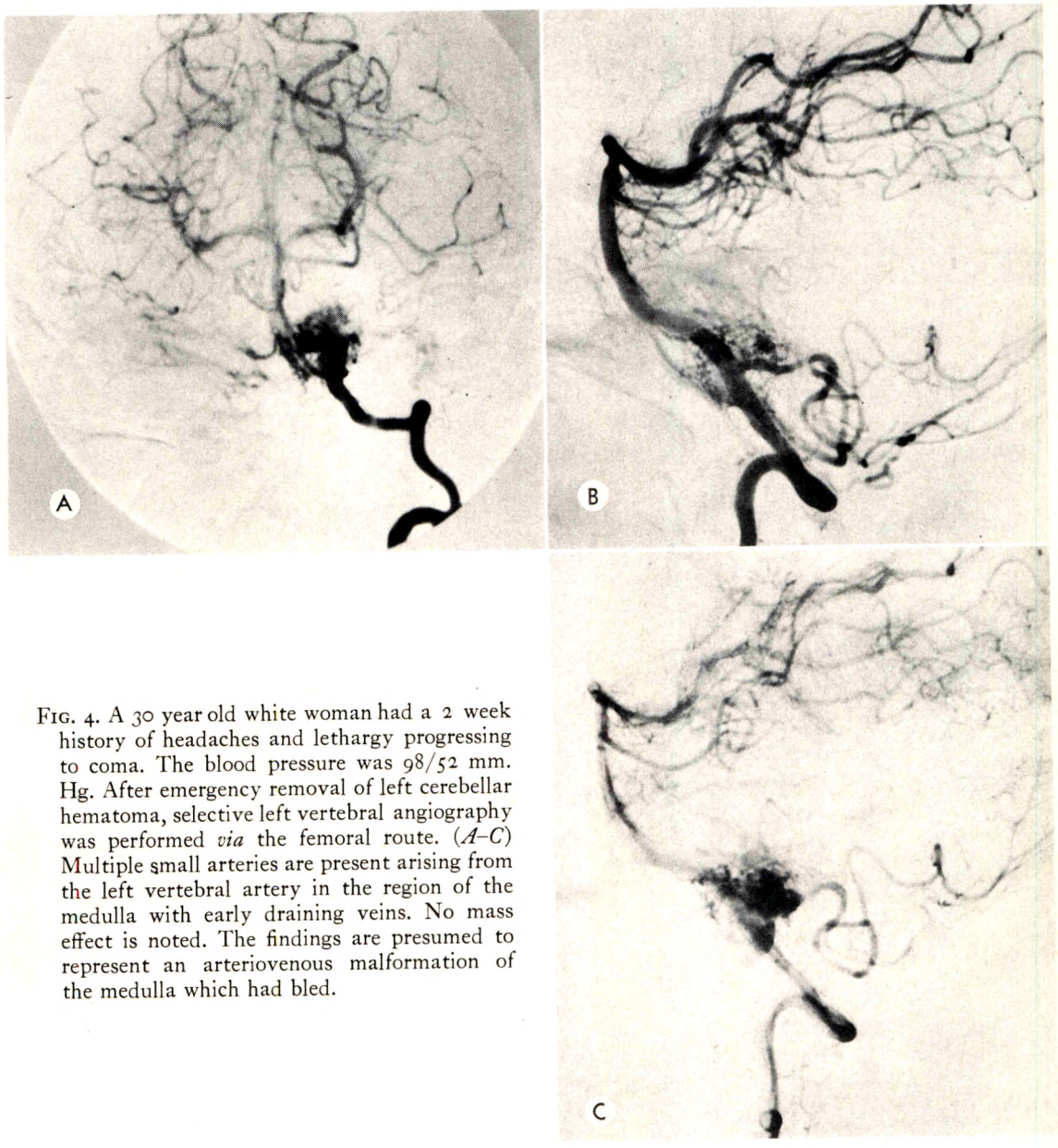

Fig. 4. A 30 year old white woman had a 2 week history of headaches and lethargy progressing to coma. The blood pressure was 98/52 mm. Hg. After emergency removal of left cerebellar hematoma, selective left vertebral angiography was performed *via* the femoral route. (*A–C*) Multiple small arteries are present arising from the left vertebral artery in the region of the medulla with early draining veins. No mass effect is noted. The findings are presumed to represent an arteriovenous malformation of the medulla which had bled.

pointed out the difficulty in distinguishing cerebellar and pontine hemorrhage clinically. The angiographic findings seem distinctive enough to separate the 2 entities. The distinction is important because pontine hemorrhage is not amenable to surgical evacuation.

Other causes of cerebellar hemorrhage include arteriovenous malformations, aneurysms, primary and metastatic tumors, trauma, and anticoagulant therapy. In the normotensive patient in whom the clinical findings are characteristic of cerebellar hemorrhage, an angiogram is strongly indicated because it may give a clinically unsuspected diagnosis.

SUMMARY

In a patient with cerebellar hemorrhage due to hypertension, deterioration may be

so rapid there is not sufficient time for radiographic studies prior to craniectomy.

In the less critically ill patient, posterior fossa angiography is the procedure of choice and is highly accurate in localizing the mass lesion.

Angiography is particularly helpful in the patient with an atypical presentation because an etiology of the hemorrhage other than hypertension may be demonstrated.

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VOL. 123, NO. 1

BASAL GANGLIA CALCIFICATION AS A LATE RADIATION EFFECT*

By YUJI NUMAGUCHI, M.D., JAMES C. HOFFMAN, JR., M.D., *and* PETER J. SONES, JR., M.D.
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VIRCHOW[15] first reported microscopic perivascular calcification of the basal ganglia in 1855. The first roentgenographic description of the symmetric calcification of the basal ganglia was reported in 1935, by both Fritzsche,[7] and Kasanin and Crank.[9] There are other reports of calcification of the basal ganglia in the literature.[1–6, 9, 12–14] In 1970, Harwood-Nash and Reilly[8] described 2 children with basal ganglia calcification following radiation therapy. In 1974, Kramer and Lee[10] briefly mentioned this condition as a result of irradiation.

The case to be presented here, we believe, is the fourth case in the English language literature of basal ganglia calcification following radiation therapy.

REPORT OF A CASE

A.S., a 9 year old white female, presented at the Medical College of South Carolina at the age of 31 months with the diencephalic syndrome. Skull roentgenograms showed evidence of increased intracranial pressure (Fig. 1, *A* and *B*). Bone roentgenograms revealed a bone age of 24 months. A cerebral angiogram demonstrated dilated ventricles and a mass in the region of the hypothalamus. Following the angiography, surgical exploration was carried out and revealed an astrocytoma involving the floor of the third ventricle and hypothalamus. The mass was partially removed and the child received postsurgical radiation therapy with supervoltage external beam 2 mev, HVL 7.8 mm. Pb, FSD 110 cm. The total dose delivered was 6,000 rads during a 6 week period, using opposing lateral 7×7 cm.^{2} ports covering the hypothalamus and basal ganglia. Following irradiation, she had no evidence of a recurrent tumor, but remained extremely small, with some intellectual limitation. Endocrine studies confirmed a growth hormone deficiency. Skull roentgenograms made 15 months after radiation therapy did not reveal any basal ganglia calcification. In November, 1972, at the age of 9 years, she was admitted to Henrietta Egleston Hospital because of growth hormone deficiency.

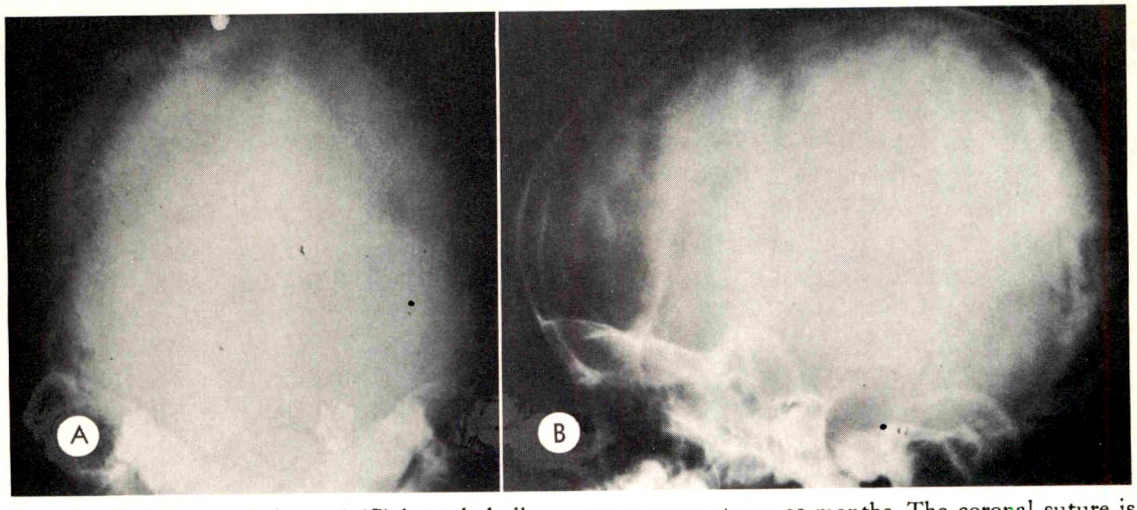

FIG. 1. (*A*) Anteroposterior and (*B*) lateral skull roentgenograms at age 31 months. The coronal suture is widened, indicating increased intracranial pressure. No evidence of basal ganglia calcification.

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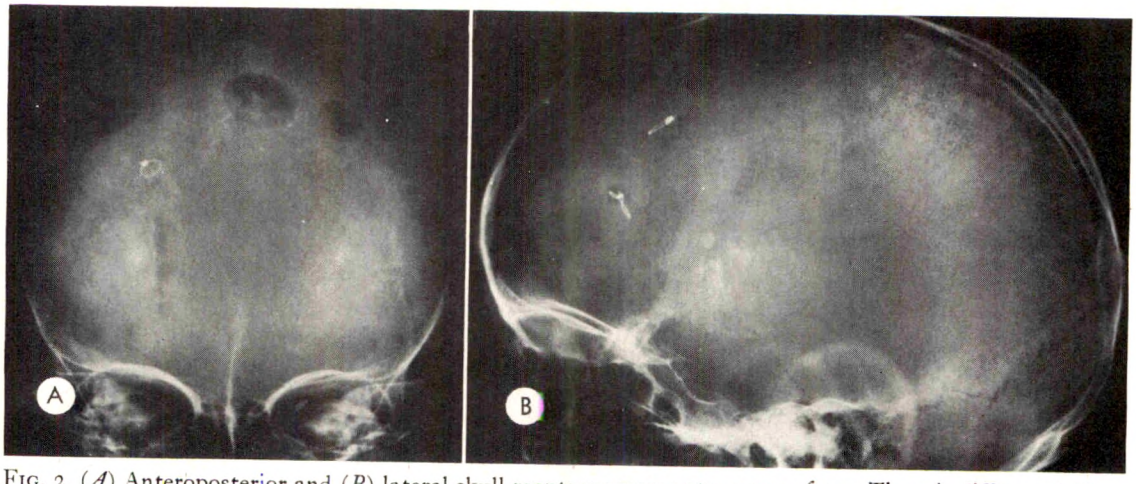

FIG. 2. (*A*) Anteroposterior and (*B*) lateral skull roentgenograms at 9 years of age. There is diffuse calcification in the region of the basal ganglia bilaterally. Frontal burr holes are noted from previous surgery.

Skull roentgenograms at this time showed diffuse calcification of the basal ganglia bilaterally (Fig. 2, *A* and *B*). A brain scan at this time was normal. In December, 1973, she was readmitted because of frontal headache and intermittent vomiting. Skull roentgenograms again revealed diffuse calcification of the basal ganglia, but no increase in the amount of calcification. A brain scan and cerebral angiogram showed recurrence of the tumor. She received additional radiation therapy using cobalt 60. Serum calcium and phosphorus levels remained normal.

DISCUSSION

Calcification of the basal ganglia associated with idiopathic hypoparathyroidism and pseudohypoparathyroidism is now a well-known entity.[4,14] Approximately 50 per cent of the patients with these entities demonstrated calcification.[2] According to Fitz *et al.*[5] patients with tuberous sclerosis may present with calcification either in the basal ganglia or paraventricular region. The instance of calcification ranges from approximately 33 per cent in children less than 5 years of age to 60 per cent in children 10 to 14 years of age. Other causes of basal ganglia calcification include familial idiopathic cerebral calcification, encephalitis, toxoplasmosis, cytomegalic inclusion disease, mental deficiency, amaurotic idiocy, and carbon monoxide or lead intoxication.

The roentgenographic appearance of basal ganglia calcification is characteristic and can in most instances be differentiated from calcification in tumors or calcification in the choroid plexus. Tumor calcification is typically unilateral and localized. Special studies such as cerebral angiography or pneumoencephalography will demonstrate a mass lesion. Choroid plexus calcification is usually located in the atrium of the lateral ventricle, and because of its location can be differentiated from basal ganglia calcification. The calcification in tuberous sclerosis may be in the basal ganglia or paraventricular region; however, pneumoencephalography will show evidence of multiple subependymal nodules, and these patients will also present with seizures, mental retardation, and cutaneous manifestations of adenoma sebaceum. The calcification in toxoplasmosis, cytomegalic inclusion disease, or inflammatory processes does not confine itself to the basal ganglia, but may be generalized in the cerebral hemispheres. Familial idiopathic cerebral calcification is frequently associated with mental deterioration, growth retardation, and epilepsy. The calcification is usually found in the cerebral cortex, cerebellum, and also in the basal ganglia.

Basal ganglia calcification following irradiation has seldom been documented in the literature. Table 1 shows 3 reported cases and our additional case report. All

Table I

REPORTED CASES OF BASAL GANGLIA CALCIFICATION FOLLOWING RADIATION THERAPY

Case No.	Author	Age (yr.)	Sex	Pathology and Site	Source, Field Size and Dose	Time Required for Calcification to Develop	Serum Calcium and Phosphorus Levels
1.	Harwood-Nash and Reilly,[8] 1970	9	F	Glioblastoma multiforme in the suprasellar region	External cobalt 60, 5×5 cm.^{2} 4,500 rads/4 weeks and 4,500 rads/4 weeks 3 years later	3 years	Normal
2.	Harwood-Nash and Reilly,[8] 1970	3	M	Histiocytosis X involving multiple areas of the calvarium	200 kv. x-ray, various ports 300 rads×3, 1,250 rads next year, and 1,700 rads following year	9 years	Normal
3.	Kramer and Lee,[10] 1974	10	M	CNS involvement of lymphocytic leukemia	External cobalt 60 Not mentioned 550 rads	10 months	—
4.	Numaguchi *et al.*, 1974	9	F	Astrocytoma in the hypothalamic region	Supervoltage 2 mev. resonant transformer, 7×7 cm.^{2} 6,000 rads/6 weeks	6 years	Normal

CNS = central nervous system.

patients were under 10 years of age with no sex predilection. The amount of irradiation varied considerably. The patient reported by Kramer and Lee[10] received 550 rads midline dose with cobalt 60 for lymphocytic leukemia, and diffuse cortical and basal ganglia calcification developed approximately 10 months later. It is difficult to estimate the total dose to the basal ganglia in the second case of Harwood-Nash and Reilly,[8] because irradiation was aimed at several different places on the calvarium over a 6 year period of time. The midline dose is thought to be less than 2,000 rads. Diffuse bilateral basal ganglia calcification was noted 9 years after the initial irradiation. The other case of Harwood-Nash and Reilly[8] was reported to have received 4,500 rads over 4½ weeks, and the same dose was repeated 2 years later for a glioblastoma multiforme involving the hypothalamus. The patient was noted to have diffuse bilateral basal ganglia calcification 3 years after the initial radiation therapy. The total irradiation dose in these patients varied considerably from less than 1,000 rads to as much as 9,000 rads. The time required for the calcification to develop ranged from 10 months to 9 years from the date of initial irradiation.

The etiology of basal ganglia calcification following radiation therapy remains obscure. We are inclined to agree with the speculation of Harwood-Nash and Reilly[8] that the vascular calcification in these patients may be due to unusual sensitivity to irradiation with resultant damage in the basal ganglia. Another cause of calcification might be delayed demyelination following irradiation, resulting from a localized allergic reaction and subsequent accumulation of abnormal metabolites as suggested by Lampert *et al.*[11]

SUMMARY

Basal ganglia calcification following radiation therapy has rarely been documented in the literature.

A case of diffuse bilateral basal ganglia calcification developing 6 years after irradiation of a hypothalamic glioma is presented.

Review of previous reports and other causes of basal ganglia calcification are discussed.

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Vol. 123, No. 1

MAGNIFICATION ANGIOGRAPHY*

IDENTIFYING THE CAPSULAR VASCULATURE OF ACOUSTIC NEUROMAS

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THE recent perfection of the small focal spot tube has enabled excellent visualization of important structures not well seen by conventional techniques.

We have recently studied several acoustic neuromas with magnification angiography and have identified abnormal clusters of vessels within the tumor confines. These vessels were confirmed surgically utilizing the dissecting microscope.

MATERIAL AND METHOD

Although selective vertebral artery angiography has been successfully performed at our hospital in more than 50 patients with acoustic neuromas, only the last 6 patients had the benefit of magnification angiography.

A preshaped No. 5 French polyethylene catheter was selectively placed into either the right or left vertebral artery. Six to 7 ml. Renografin 60 per cent was injected intra-arterially, using an automatic injector at a flow rate of 3 ml. per second. The film sequence extended over a period of 10 seconds, exposing 2 films every second for the

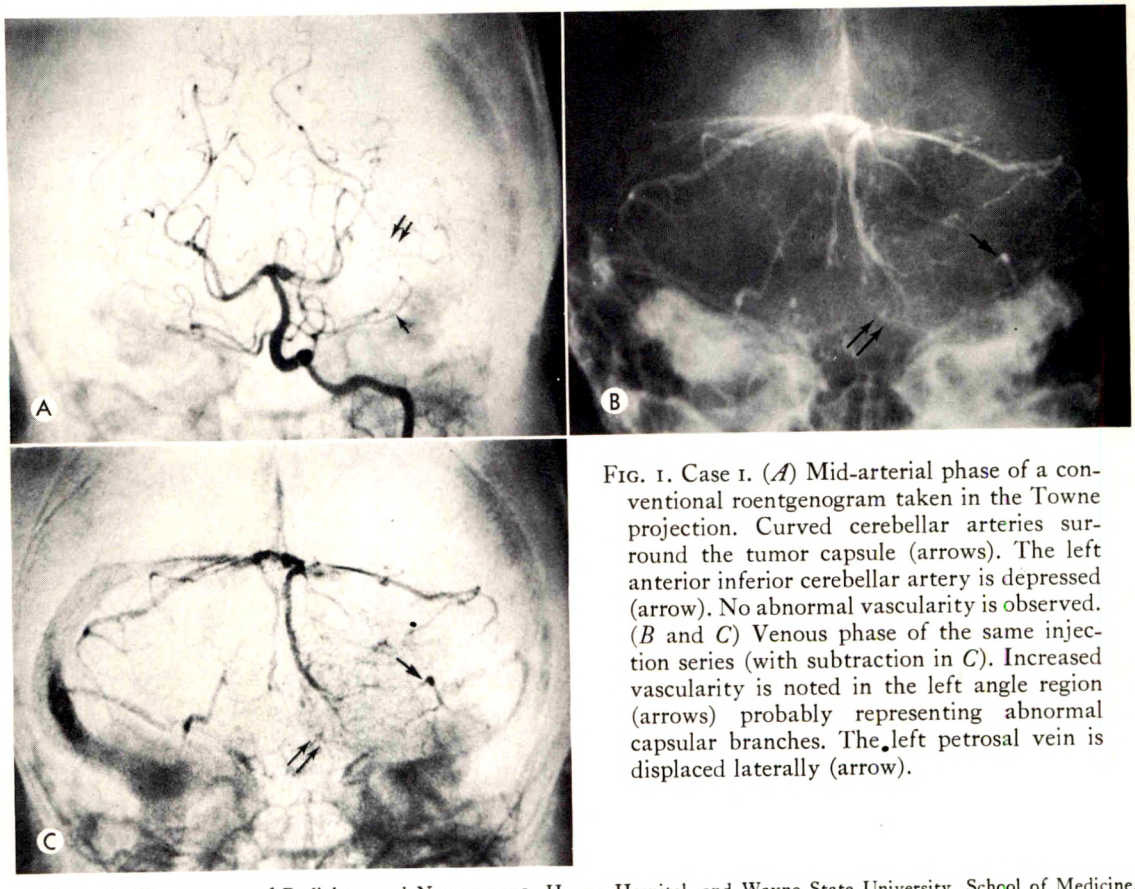

FIG. 1. Case 1. (*A*) Mid-arterial phase of a conventional roentgenogram taken in the Towne projection. Curved cerebellar arteries surround the tumor capsule (arrows). The left anterior inferior cerebellar artery is depressed (arrow). No abnormal vascularity is observed. (*B* and *C*) Venous phase of the same injection series (with subtraction in *C*). Increased vascularity is noted in the left angle region (arrows) probably representing abnormal capsular branches. The left petrosal vein is displaced laterally (arrow).

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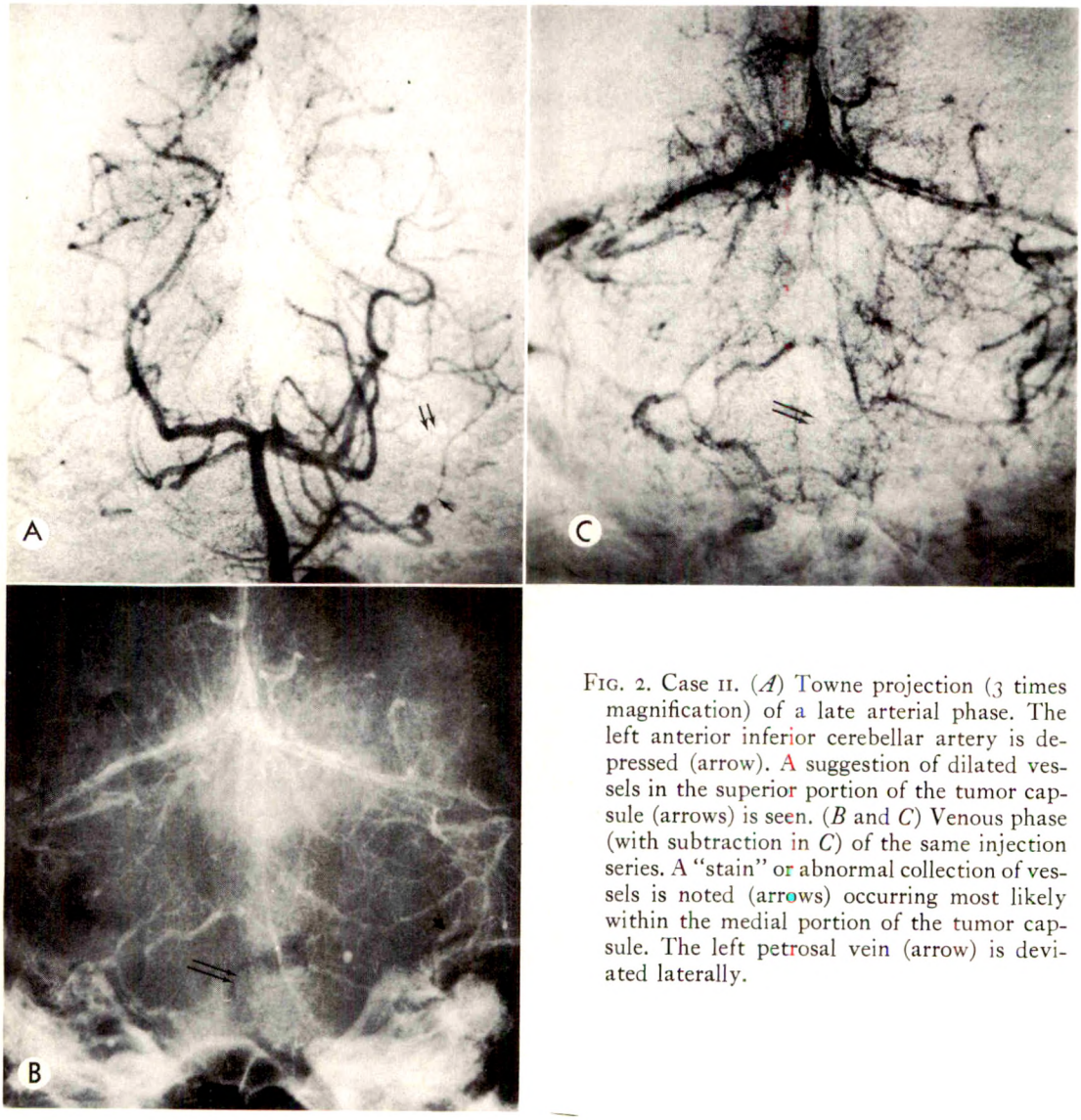

FIG. 2. Case II. (*A*) Towne projection (3 times magnification) of a late arterial phase. The left anterior inferior cerebellar artery is depressed (arrow). A suggestion of dilated vessels in the superior portion of the tumor capsule (arrows) is seen. (*B* and *C*) Venous phase (with subtraction in *C*) of the same injection series. A "stain" or abnormal collection of vessels is noted (arrows) occurring most likely within the medial portion of the tumor capsule. The left petrosal vein (arrow) is deviated laterally.

initial 3 seconds, then 1 film each second for the remainder of the study.

Magnification factors include the use of Siemens 0.2 mm. microfocus tube, high-speed film, removal of the grid, kilovoltage in the 95–100 range, and milliampere-second averaging between 10 and 12. The elevating Schonander table can be raised 40 inches to produce at least 3 times magnification, providing the patient's head is against the lower tube border.

Transfacial and Towne projections gave the most informative views.

DISCUSSION

Acoustic neuromas continue to provide physicians with a difficult diagnostic challenge.

Positive auditory testing, particularly discriminatory hearing loss, abnormal electronystagmography, characteristic laminagraphy, and myelography changes[3,4] have been well described pathognomonic findings of a cerebellopontine angle mass.

Vertebral angiography has increased our understanding of the vascular displacements caused not only by the neuroma,

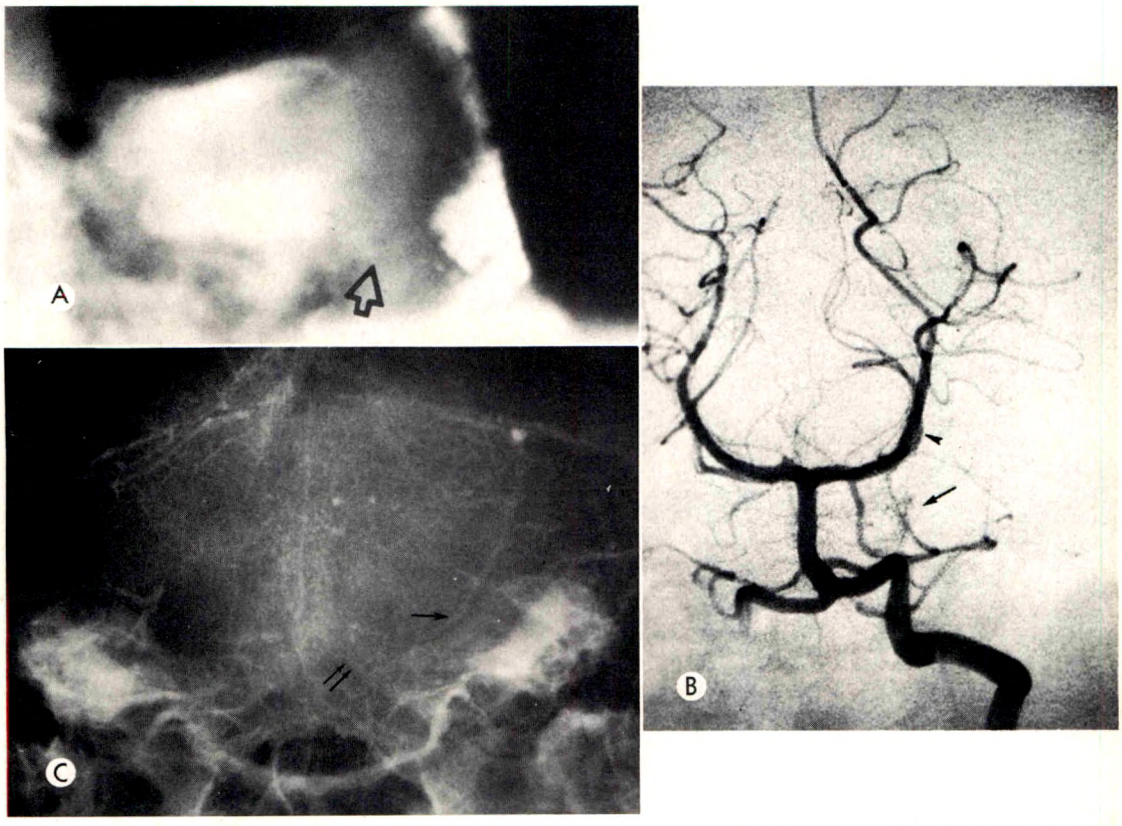

Fig. 3. Case III. (*A*) Anteroposterior tomogram indicating the presence of a smooth left angle tumor (arrow) displacing the Pantopaque medially. (*B*) Towne projection (3 times magnification) of the arterial phase. Abnormal tumor capsular vessels (arrow) are noted. The left superior cerebellar artery is pushed medially and upwards (arrowhead). (*C*) Venous phase of the same injection series. The tumor capsular vessels (arrows) are still apparent. The left petrosal vein is displaced laterally (arrow).

but by associated cerebellar and brain stem changes. The occasional "hooker" diagnosis in angle masses such as aneurysms, hemangioblastomas, meningiomas, eccentric brain stem gliomas, epidermoids, and metastatic tumors may be shown by this diagnostic modality.

Sophisticated microscopic operative techniques depend upon tumor size and include craniotomy by suboccipital, translabyrinthine, middle fossa and combined approaches. Choosing the proper approach necessitates a detailed preoperative evaluation of the boundaries of the neuroma.

Figure 1*A* demonstrates the typical circumscribed vessels which outline the tumor. Most neuromas present surgically as rounded masses having a central hypovascular core and a surrounding capsule. It is the capsular portion which contains numerous vessels and which often becomes adherent to adjacent structures such as the brain stem, cerebellar hemisphere and arachnoidal tissue.

The "stain" seen in Figure 1, *B* and *C* was caused by increased vascularity within the capsule. In our series these capsular vessels were best seen in the Towne and transfacial views with the aid of magnification techniques (Fig. 2, *A–C*; and 3, *A–C*).

The last 2 cases (Fig. 4, *A–C*; and 5, *A–D*) definitely show fine capsular vessels that were demonstrated with magnification angiography, but were difficult to delineate with conventional methods.

Meningioma stains are more homoge-

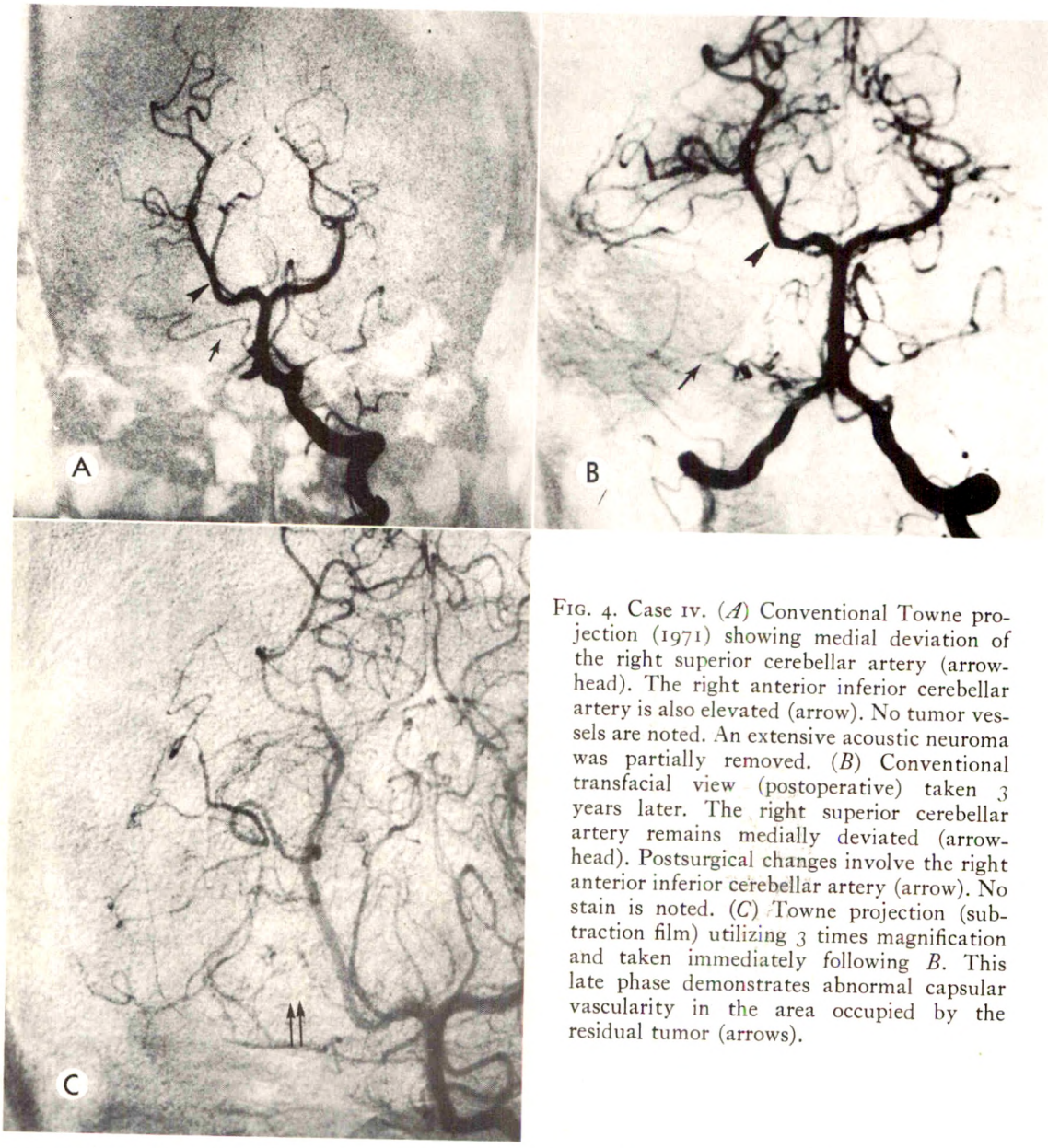

FIG. 4. Case IV. (*A*) Conventional Towne projection (1971) showing medial deviation of the right superior cerebellar artery (arrowhead). The right anterior inferior cerebellar artery is also elevated (arrow). No tumor vessels are noted. An extensive acoustic neuroma was partially removed. (*B*) Conventional transfacial view (postoperative) taken 3 years later. The right superior cerebellar artery remains medially deviated (arrowhead). Postsurgical changes involve the right anterior inferior cerebellar artery (arrow). No stain is noted. (*C*) Towne projection (subtraction film) utilizing 3 times magnification and taken immediately following *B*. This late phase demonstrates abnormal capsular vascularity in the area occupied by the residual tumor (arrows).

neous than the stippled appearance of the neuroma. Abnormal meningeal vessels also distinguish these tumors.

Epidermoid tumors have not been reported to have abnormal capsular vascularity and pathologically do not show such a finding.

Although neuromas may elevate the anterior inferior cerebellar artery, depression of this vessel was confirmed surgically in 4 of the cases presented.

Lateral displacement of the petrosal vein was associated with tumor involvement of the semilunar ganglion.

SUMMARY

Five cases of acoustic neuromas studied angiographically are presented.

Magnification techniques enhance the visualization of the fine capsular vessels of

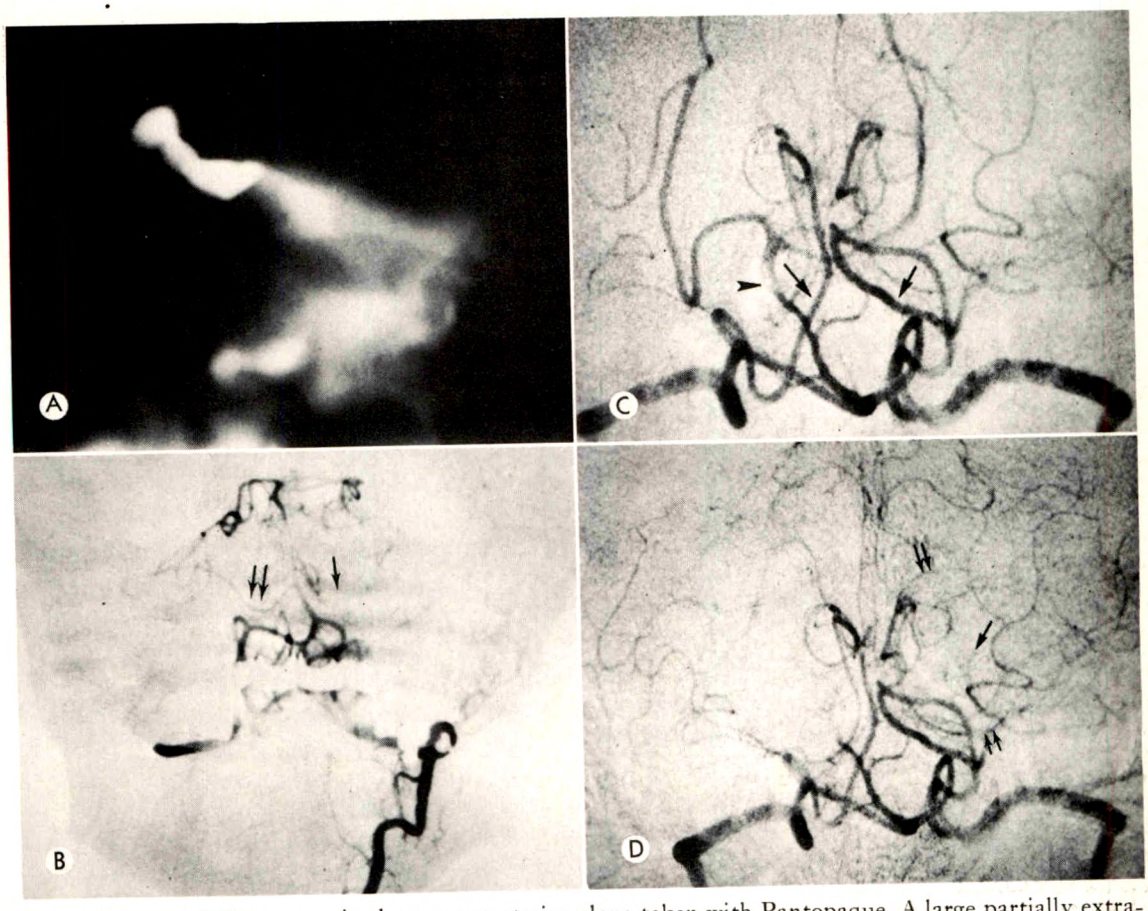

Fig. 5. Case v. (*A*) Tomogram in the anteroposterior plane taken with Pantopaque. A large partially extracanalicular acoustic neuroma is demonstrated. The lack of any impression upon the superior portion of the contrast material is against involvement of the semilunar ganglion. (*B*) Conventional transfacial view. The left anterior inferior cerebellar artery (arrow) is poorly seen when compared to the right (arrows). No stain is noted. (*C*) Towne projection (3 times magnification) of the early arterial phase, taken immediately following *B*. The basilar artery (arrowhead) and the 2 posterior inferior cerebellar arteries (arrows) are noted. (*D*) Towne projection (3 times magnification) of the late arterial phase. The abnormal capsular vessels (arrow) and the circumscribed branches of the left posterior inferior cerebellar artery surrounding the tumor (arrows) are now apparent.

these tumors. When shown, these abnormal vessels are probably pathognomonic of a neuroma.

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DOSIMETRY OF SPHERICAL Sr^{90}-Y^{90} β RAY EYE APPLICATORS*

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VARIOUS morbid conditions of the eye, *i.e.*, corneal ulceration, vascularization pterygium, tumors of the cornea and eyelid, etc., have been treated with Sr^{90}-Y^{90} eye applicators during the past 2 decades. Plane plaques, first described by Fridell *et al.*[4,5] are being widely used in North America, whereas spherical shaped applicators developed by Lederman[13,14] and Ainslie *et al.*[1] are used in the U.K. The dosimetry of plane plaques has been extensively studied and has been reported in the literature.[2,3,6–8,11,12,16,19,20,24,26] The dosimetry of spherical applicators has not been so widely studied due to the geometry involved. Sinclair and Trott[18] have reported results on the dosimetry of earlier forms of these spherical applicators. The dosimetry of spherical applicators specially designed for irradiation of the conjunctival sac has been reported by Lederman and Jones.[15] Since then, however, spherical sources have been improved and are now metallic, with silver serving both as the main backing and as covering material. Plastics are no longer used as the backing material.[17] Jones and Dermentzoglou[9] have studied the dosimetry of these modified sources recently. However, all earlier workers have used a scintillation detector 3 mm. in diameter and 0.5 mm. thick. The use of such a detector tends to average out the dose and to modify the contours of the isodose curves. Hence, it was decided to study afresh the dosimetry of spherical applicators in detail.

Dosimetry was done on 3 types of sources (SIA.1, SIA.3 and SIA.6) routinely, supplied by Radiochemical Centre, Amersham.[17] For standardizing dosimetric techniques a plane plaque type Sr^{90}-Y^{90} eye applicator type RA.1 was used.[25] The dimensions and other physical characteristics of these sources are presented in Table 1.

SPHERICAL EXTRAPOLATION CHAMBER

Absolute dose measurements of these applicators cannot be done using the conventional extrapolation chamber, as there remains a considerable air gap between the source surface and the sensitive volume of the chamber because of the curvature of the source. In order to obviate this difficulty, a suitable modification was made to the extrapolation chamber. The modified extrapolation chamber is shown in Figure 1. The upper electrode of the extrapolation chamber was a thin strip of aluminized mylar given a spherical shape by pressing it on a polystyrene insulator having a radius of curvature of 15 mm., which is the same as the radius of curvature of the SIA.1 and SIA.3 sources. A similar electrode with radius of curvature 10 mm. was also made to match the SIA.6 type source. The central electrode is an aluminum wire of 1.6 mm. diameter. In this construction, no guard ring could be provided. It was assumed that the volume enclosed between the upper surface of the central electrode, the aluminized mylar and the wall of the solid insulator is the sensitive volume of the chamber. This volume may not contribute completely to ion collection. Corners of the volume will not have strong enough fields to give 100 per cent ion collection efficiency. This tends to reduce the current obtained in the chamber. The solid side walls of the polystyrene which delineate the sensitive volume on all sides, however, tend to increase the ion current due to the extra amount of side scatter as compared to the air scatter in the normal plane extrapolation chambers. These two

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TABLE I

PHYSICAL CHARACTERISTICS OF STRONTIUM 90 OPHTHALMIC APPLICATORS

Source Type	Activity Content (millicuries)	Construction	Dose Rate (rad/s.)	Type of Extrapolation Chamber
SIA.1 (1086)	10	Spherical cap of 23 mm. diameter and 15 mm. radius of curvature; active disk 18 mm. in diameter	2.0±0.1	Spherical: 15 mm. radius of curvature
SIA.3 (1109)	9	Spherical cap of 23 mm. diameter and 15 mm. radius of curvature; active annulus 18 mm. outer diameter and 6 mm. inner diameter	1.6±0.1	Spherical: 15 mm. radius of curvature
SIA.6 (1122)	10	Spherical cap of 15 mm. diameter and 10 mm. radius of curvature; active disk 12 mm. in diameter	6.5±0.2	Spherical: 10 mm. radius of curvature
RA.1 (736)	50	Plane source of 12.7 mm. diameter; active diameter: 6.0 mm.; source covered with 10 mils of aluminum and 2 mils of stainless steel	19.3±0.5 19.5±0.5	Spherical: 15 mm. radius of curvature Plane

effects are opposed to each other and are estimated to be small in magnitude and thus the resultant difference between this chamber and the conventional extrapolation chamber is expected to be small. Values of ionization current were obtained for various separations between the mylar surface and the upper surface of the central electrode. The slope of this curve at zero

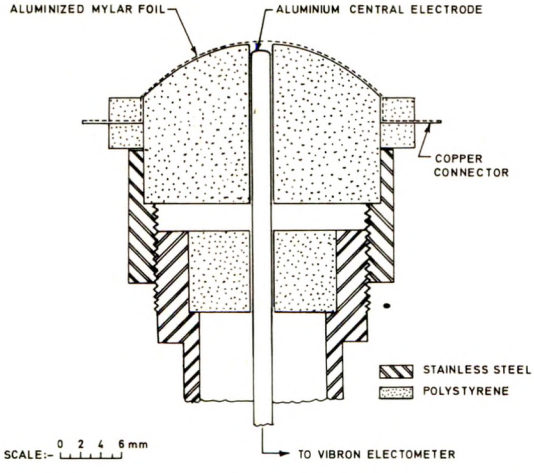

FIG. 1. The cross section of the modified extrapolation chamber. The top spherical surfaces have 15 mm. and 10 mm. as radii of curvatures, so that the spherical eye applicators fit exactly on the extrapolation chambers.

volume was used to evaluate the dose rate at the surface of the spherical applicator. Measurements were made on the 3 spherical sources described earlier. The surface dose rate from the plane applicator was also determined using both the spherical extrapolation chamber described above and a conventional parallel plate extrapolation chamber. It was found that no significant difference in the readings shown by the two extrapolation chambers could be detected, which shows the validity of the assumptions made in the case of spherical extrapolation chamber.

DOSIMETRY DATA

The dose rates measured with the spherical extrapolation chambers at the surfaces of the various spherical applicators are presented in the last column of Table 1. Other physical information such as the relative variation of dose rate across the surface, the depth dose data, and the isodose distributions were obtained by using single emulsion films.

In order to reproduce the spherical geometry conditions under which the applicators are used, wooden spheres with radii of curvatures 15 mm. and 10 mm.

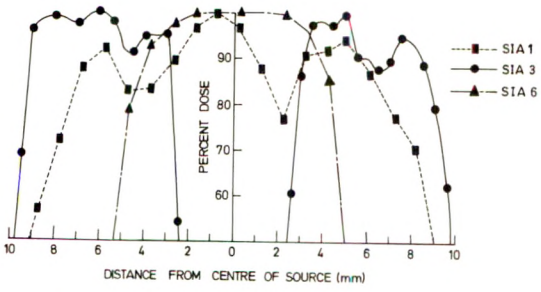

FIG. 2. The variations of the dose on the surface of spherical applicators.

were specially used. Spherical grooves of 3 mm. width and 3.75 mm. depth were cut into the wooden spheres. These grooves were filled in by a stack of black polythene sheets and Ilford N 550 film strips cut into suitable sizes. The Ilford N 550 film has a linear dose density relationship for β rays up to an optical density of 3.

The polythene separators were used to get an effective density of unity, as it has already been shown[21] that the material to be used in tissue dose measurements should simulate the tissue not only in its electron content but also in its density. Black polythene strips and wood were selected specially for these exposures, as it was recently shown[23] that the use of other transparent and translucent materials may cause errors due to the difference in response of the films to β rays and to the Cerenkov radiation produced when β rays pass through the medium. In order to ensure the centering of the source on the film, suitable cylindrical devices were constructed and employed.

The distribution of the surface dose along a spherical diameter was obtained from the top film of the stack which gives an autoradiograph of the source. Autoradiographs along 6 diameters each separated from the other by 30° were taken and the dose variations were obtained by scanning for the optical density with a 0.5 mm. densitometer aperture. The maximum variations observed for each of the 3 sources used are shown in Figure 2. It can be seen from this figure that the specific surface activity is not at all uniform and varies by as much as 20 per cent for the SIA.1 type applicator.

The doses at various depths as well as the isodose curves were obtained from the density scans of the exposed stack of film strips. The average values of the depth dose data and the variations in them are shown in Figure 3, and the isodose curves obtained are presented in Figure 4.

DISCUSSION

From Figure 3 it may be noted that the percentage dose for the spherical applicator is higher than for the plane applicator, indicating a focussing effect for beta rays from spherical applicators. For comparison, the central axis depth dose data obtained by Sinclair and Trott[18] and Jones and Dermentzoglou[9] are also presented in the same figure. From these data it is seen that at initial depths they have obtained higher values of depth doses and at larger depths our data show higher values. These differences could be considered to be due to inaccuracies of the film dosimetry. The accuracy of dosimetry using films has been discussed earlier by many workers.[3,6,10,16,19,24]

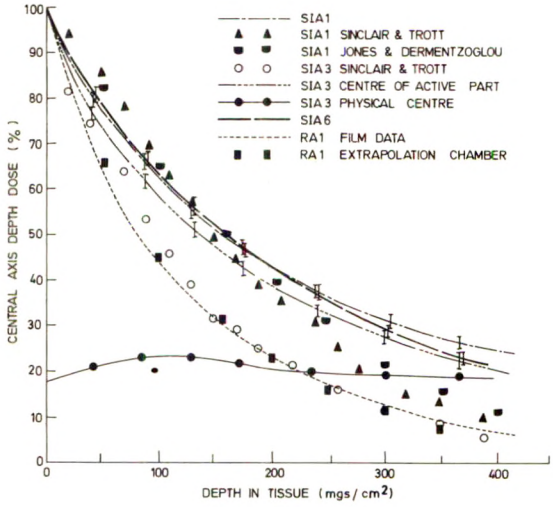

FIG. 3. Central axis depth dose data for the spherical β ray eye applicators. Data of Sinclair and Trott[18] and Jones and Dermentzoglou[9] are also presented. The data for plane RA.1 applicator as obtained from extrapolation chamber and the Ilford N 550 films are given for comparison.

In order to ensure that the data obtained using films are really correct, the central axis depth dose for a plane plaque Sr^{90}-Y^{90} applicator (type RA.1) was obtained by the film method as well as by an extrapolation chamber. These data as presented in Figure 3 show that the film method gives the data to within ± 5 per cent. Thus, the large difference between our data and those of Sinclair and Trott[18] cannot be ascribed to inaccuracies of the film method. This difference can be explained as follows: Sinclair and Trott used an old type of applicator which was backed by plastic. The difference between the data of Jones and Dermentzoglou[9] and Sinclair and Trott[18] can be accounted for by this fact. Differences between our data and those of Jones and Dermentzoglou[9] may be due to a considerably larger size detector being used by the latter which could not be matched exactly to the spherical geometry. The difference could in part be also due to their use of perspex of density 1.19 gm./cm.^{3} instead of unit density material.

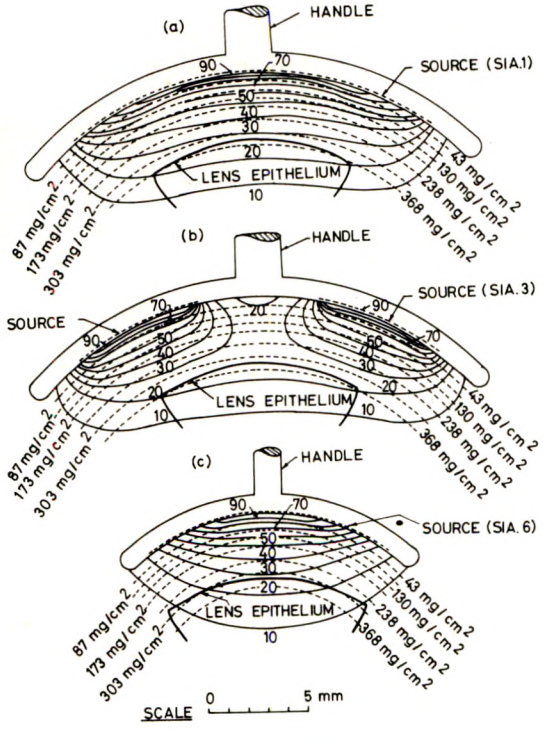

Fig. 4. The isodose curves for (a) SIA.1, (b) SIA.3 and (c) SIA.6 types of spherical applicators are shown, assuming surface dose rate as 100 per cent.

From the isodose curves presented in Figure 4 it is seen that some portions of the 20 per cent and 10 per cent isodose curves lie at larger depths than 370 mg./cm.^{2} which was the maximum depth at which our film emulsion was placed. By extrapolation of the central axis depth dose data the depths corresponding to 20 per cent and 10 per cent were obtained and these points were joined to the points obtained from the lowest film. It may further be noted from the isodose curves for applicators SIA.1 and SIA.3 that even though the surface dose variations are very large, the dose variation at various depths (except for very superficial depths), was much smoother. Since in clinical work, it is of interest to know the average dose at any depth, measurements were carried out for 3 different diameters of each applicator and the average values are presented in Figure 4. This averaging process has also contributed to the smoothness of these isodose curves. The dose under the central inactive area of the SIA.3 applicator is about 15 to 20 per cent of that under the active area. Compared to Sinclair and Trott's[18] data, this is a low value. Some of their larger values could be ascribed to the averaging over a large area of the detector. The isodose distributions for the applicator SIA.6 are nearly the same as those for the SIA.1 but for its smaller size.

In all these isodose curves the position of the eye lens epithelium is shown. In case of SIA.1 and SIA.3 type of applicators the lens epithelium receives a nearly uniform dose. The per cent doses at lens epithelium compared to the surface doses are 30 and 26, respectively, for SIA.1 and SIA.3 applicators. For the SIA.6 applicator the per cent dose is 28 at the center of the lens and 10 at the periphery. These values are larger than the values of about 15 per cent obtained by Sinclair and Trott[18] and Jones and Dermentzoglou.[9] Using our values, the probabilities of radiation cataract induction defined as an integral of the product of

TABLE II

PROBABILITIES OF RADIATION CATARACT FOR 100 RADS OF SURFACE DOSE

S. No.	Type of Applicators	Position	Radiation Cataract Probability (rad. cm.^{2}/10^5 cells)
1.	RA.1	Centered at limbus	310
		Centered at corneal center	26.1
2.	SIA.1	Centered at corneal center	723
3.	SIA.3	Centered at corneal center	722
4.	SIA.6	Centered at corneal center	447

area of irradiation, the radiation dose and the radiosensitivity of the irradiated region,[22] were estimated for each of the applicators and are presented in Table II. For comparison, the probability of radiation cataract resulting when the RA.1 type plane applicator is used (1) for treatment at the limbus and (2) for treatment at the center of the cornea is also presented. The data indicate that for the spherical applicators the probability of radiation cataract induction is larger than for RA.1 type of applicator. This is true because of the considerably larger active size of these applicators which irradiates practically the whole eye lens epithelium to a uniformly large dose. These facts should be borne in mind when planning therapy of eye lesions.

SUMMARY

A modification of the conventional extrapolation chamber to perform absolute dose measurements from surfaces of spherical β applicators (type SIA.1, SIA.3, SIA.6) is described.

A stack of Ilford N 550 films has been used in a spherical geometry to obtain the variation of surface dose, the depth dose data and the isodose curves.

The results obtained are compared with data available in the literature.

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CONTROL BY IRRADIATION ALONE OF NONFIXED CLINICALLY POSITIVE LYMPH NODES FROM SQUAMOUS CELL CARCINOMA OF THE ORAL CAVITY, OROPHARYNX, SUPRAGLOTTIC LARYNX, AND HYPOPHARYNX*

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THERE has been a widely held conviction that cervical lymph node metastases are more resistant to irradiation than the primary lesion from which they arise. This concept has been responsible for almost total dependence on surgery for their management. However, the respective roles of surgery and radiation therapy in treatment for cervical lymph node metastases have been under analysis in the recent past. Publications from the M.D. Anderson Hospital and Tumor Institute[2,5–7] and other institutions[3,9] have shown:

(1) The effectiveness of elective treatment of the neck by external irradiation therapy for subclinical disease.

(2) The diminution of recurrent disease in the radically dissected neck by pre- or postoperative irradiation.

The purpose of this essay is to analyze the results in patients with clinically positive cervical lymph node(s) treated with external irradiation alone.

MATERIAL AND METHOD

From January 1948 through December 1967, 344 patients with previously untreated primary lesions and clinically positive cervical lymph node metastases staged N_1, N_{2A}, and N_{2B} were treated at M. D. Anderson Hospital with external irradiation alone (Table I). All patients had histologically proven squamous cell carcinomas, located in the anterior two-thirds of the tongue, floor of mouth, gingivae, anterior faucial pillar, retromolar trigone, soft palate, uvula, tonsillar fossa, base of tongue, pharyngeal walls, supraglottic larynx, and hypopharynx. The treatment policies for the primary lesions determined coverage of the nodes in the portals treating the primary lesions. Nineteen patients were planned for postirradiation neck dissection, but are included in the analysis since the contemplated surgery was not performed. The results of the nodal irradiation (Table II) could not be evaluated in 161 patients for the following reasons:

TABLE I

CLINICAL STAGING OF CERVICAL LYMPH NODE METASTASES

Stage	Description
N_0	No clinically positive lymph node
N_1	Single clinically positive lymph node ≤ 3 cm. in diameter
N_{2A}	Single clinically positive lymph node > 3 cm. in diameter
N_{2B}	Multiple clinically positive ipsilateral lymph nodes
N_{3A}	Unilateral fixed lymph node(s), clinically positive
N_{3B}	Clinically positive bilateral lymph nodes, fixed or not fixed

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TABLE II

PATIENT DISTRIBUTION BY SITES AND REASONS FOR EXCLUSION
SQUAMOUS CELL CARCINOMA OF THE ORAL CAVITY, OROPHARYNX, SUPRAGLOTTIC LARYNX AND HYPOPHARYNX

(January 1948 through December 1967)
(Analysis January 1972)

	Total No. Patients	External Irradiation to Neck not Completed	Primary Lesion Uncontrolled when Node Recurred	Survival Under 24 Months,* Neck NED	New Manifestation of Disease Outside Treatment Field with Partial Neck Irradiation	Total No. Excluded	Study Group
Anterior 2/3 of Tongue	29	2	13	4	2	21	8
Floor of Mouth	16	0	2	3	1	6	10
Upper Gum	3	0	1	0	0	1	2
Lower Gum	12	0	4	0	0	4	8
Buccal Mucosa	12	1	4	2	0	7	5
Retromolar Trigone-Anterior Faucial Pillar	51	1	9	10	1	21	30
Soft Palate	13	0	2	4	0	6	7
Base of Tongue	51	3	17	6	0	26	25
Tonsillar Fossa	62	0	15	9	0	24	38
Pharyngeal Wall	38	2	13	6	2	23	15
Supraglottic Larynx	28	1	2	3	1	7	21
Hypopharynx	29	1	11	2	1	15	14
Total	344	11	93	49	8	161	183

* Patient died within 24 months after treatment from either primary failure, distant metastases, complications, intercurrent disease or second primary lesions, but without cervical lymph node metastases.

1. Failure to complete irradiation (11 patients).
2. Recurrence of the primary lesion at the time recurrent disease appeared in the neck (93 patients). Therefore, further seeding is a possibility.
3. Forty-nine patients died in less than 24 months after treatment with no evidence of disease in the neck. These patients were still exposed to a significant risk of neck recurrence. Eighty-five per cent of the recurrences of neck disease appeared within 2 years.
4. Eight patients with partial neck irradiation developed new manifestation of cervical lymph node metastasis outside the treatment field within 2 years of initial treatment. A radical neck dissection was done and, therefore, the irradiated area, although still at risk, could not be evaluated.

The remaining 183 patients, all of whom were treated 4 years or more prior to analysis in January 1972, form the study group.

Until 1955, treatment was administered by kilovoltage; subsequently it was delivered by megavoltage from Co^{60}, 18 MeV electron beam or 22 MeV photon beam. To the majority of patients, 1,000 rads per week were given with the exception of a few patients with large fields, particularly if the larynx was included, who were treated at a rate of 850 rads per week.

The treatment plannings were an ipsilateral field only, parallel opposed fields with equal or unequal loading, wedge pair, parallel opposed fields with ipsilateral boost. The total doses ranged from 2,000

rads to more than 8,000 rads. In order to provide an analyzable number of cases, the doses were grouped around 3 levels; 5,500 rads; 6,500 rads; and greater than 6,500 rads. The doses to the lymph nodes were calculated retrospectively using the transverse diameters recorded in the treatment chart, usually taken at the SSD of the treatment fields for the primary lesion. The pattern of metastasis from these primary lesions is such[4] that the involved lymph node or lymph nodes generally lie within the treatment field for the primary lesion. When the lymph node or lymph nodes were located at the margin or partially outside the treatment field for the primary lesion or if the dosimetric information was insufficient, no attempt was made to estimate the dose to these lymph nodes.

Of the 183 patients, 76 (52 N_1, 5 N_{2A} and 19 N_{2B}) had treatment only to that part of the neck included within the treatment field of the primary lesion. The remaining 107 patients received treatment to at least the entire ipsilateral neck and usually to the entire neck bilaterally by means of a single lower anterior field abutting the margins of the treatment fields for the primary lesion.

RESULTS

The planned neck dissection was not done in 7 N_1 and 12 N_2 patients who had lesions of the supraglottic larynx, hypopharynx, and pharyngeal walls. The reason not to carry out the planned neck dissection was due to the total or almost total regression of the palpable disease at the end of treatment. The surgeon then chose to observe these patients since they had no evidence of disease at their first return visit. Although a recurrence did not develop in all of the 19 patients, 12 experienced recurrence, at which time efforts directed toward salvage were successful in only half of the patients.

Failure rates to control cervical lymph node metastases are shown by anatomic site in Tables III, IV, V, VI, and VII. Table VIII shows the results for all anatomic sites according to the radiation dose received by the lymph node(s). A scheme of rapid treatment with 5 daily fractions of 400 rads was found to be ineffective early in the study period (50 per cent recurrence) and these patients were excluded from the final tabulation of Table VIII, although they appear in the individual site Tables. Eleven of 18 failures in the N_1 stage with conventional treatment and 13 of 28 failures in the N_2 stage are in those patients in whom the lymph node was marginally covered or the dose could not be accurately determined. Most of these patients (Tables V, VI, and VII) had lesions of the supraglottic larynx, hypopharynx and pharyngeal

TABLE III

EVOLUTION OF NECK DISEASE IN LESIONS OF THE ANTERIOR TWO-THIRDS OF TONGUE, FLOOR OF MOUTH, UPPER GUM, LOWER GUM, BUCCAL MUCOSA, RETROMOLAR TRIGONE, ANTERIOR FAUCIAL PILLAR AND SOFT PALATE

(January 1948 through December 1967)
(Analysis January 1972)

N Stage	Total No. of Patients	Failure Within* Treatment Field	Surgical Salvage† Within Treatment Field	Ultimate Failures
N_1	42	8/42 (19%)	3/8	5/42
N_2	28	10/28 (36%)	3/7	7/28

* Failures/Total treated.
† Successful neck dissection/Total neck dissection.

TABLE IV

EVOLUTION OF NECK DISEASE
TONSILLAR FOSSA AND BASE OF TONGUE

(January 1948 through December 1967)
(Analysis January 1972)

N Stage	Total No. of Patients	Failure Within* Treatment Field	Surgical Salvage† Within Treatment Field	Ultimate Failures
N_1	32	5/32 (15.5%)	1/3	4/32
N_2	31	12/31 (39%)	3/9	9/31

* Failures/Total treated.
† Successful neck dissection/Total neck dissections.

TABLE V

EVOLUTION OF NECK DISEASE
PHARYNGEAL WALLS

(January 1948 through December 1967)
(Analysis January 1972)

N Stage	Total No. of Patients	Failure Within* Treatment Field	Surgical Salvage† Within Treatment Field	Ultimate Failures
N_1	6	1‡/6 (17%)	1/1	0/6
N_2	9	2§/9 (22%)	1/2	1/9

* Failures/Total treated.
† Successful neck dissection/Total neck dissections.
‡ One patient with marginal coverage or unable to calculate dose.
§ Two patients with marginal coverage or unable to calculate dose.

TABLE VI

EVOLUTION OF NECK DISEASE
SUPRAGLOTTIC LARYNX

(January 1948 through December 1967)
(Analysis January 1972)

N Stage	Total No. of Patients	Failure Within* Treatment Field	Surgical Salvage† Within Treatment Field	Ultimate Failures
N_1	13	3‡/13 (23%)	2/3	1/13
N_2	8	2§/8 (25%)	1/2	1/8

* Failures/Total treated.
† Successful neck dissection/Total neck dissections.
‡ One patient with marginal coverage or unable to calculate dose.
§ Two patients with marginal coverage or unable to calculate dose.

TABLE VII

EVOLUTION OF NECK DISEASE
HYPOPHARYNX

(January 1948 through December 1967)
(Analysis January 1972)

N Stage	Total No. of Patients	Failure Within* Treatment Field	Surgical Salvage† Within Treatment Field	Ultimate Failures
N_1	7	4/7 (57%)	2/3	2/7
N_2	7	2‡/7 (28.5%)	1/2	1/7

* Failures/Total treated.
† Successful neck dissection/Total neck dissections.
‡ One patient with marginal coverage or unable to calculate dose.

walls. For these sites the fields are carefully tailored to include a minimum of normal structures. This tailoring results in the marginal placement of nodal metastases with respect to the treatment field for the primary lesion. The failure rates in those patients with good coverage and a known dose to the node(s) are 8.5 per cent (7/83) for N_1 and 21.5 per cent (15/70) for N_2.

When a recurrence was noted, some form of neck dissection was performed (40 of 49 patients). Eighteen of the 40 patients were salvaged by such a procedure. The operative successes were equal, *i.e.*, 9 N_1, 9 N_2, in both the lymph node staging groups.

DISCUSSION

N_1 nodal disease refers to a single movable lymph node no more than 3 cm. in diameter, usually 1 to 2 cm. in diameter. The lymph node size in this group is, therefore, fairly homogeneous. The node(s) in stages N_{2A} and N_{2B} have a wide spectrum of

TABLE VIII

FAILURES IN IRRADIATED FIELDS*
PRIMARY LESION CONTROLLED; MINIMUM 4 YEAR FOLLOW-UP

(January 1948 through December 1967)
(Analysis January 1972)

N Stage	Total No. of Patients	Fast Treatment	Conventional Treatment					
		400 r×5	Total Failures, All Conventional Treatment	Marginal Coverage or Unable to Calculate Exact Dose	Known Dose (rads)			
					5,500	6,500	>6,500	Total
N_1	100	3/6	18/94 (19%)	11†	1/8	2/37	4/38	7/83 (8.5%)
N_2	83	—	28/83 (34%)	13‡	2/3	2/23	11/44	15/70 (21.5%)

* Failures/Total treated.
† Of the 18 N_1 failures (Conventional Treatment).
‡ Of the 28 N_2 failures.

tumor volume. An N_{2A} lymph node is at least 3 cm. in diameter, often 9 to 10 cm. in diameter. Some lymph nodes that are fixed to skin or connective tissue, but are otherwise movable, are staged N_{2A}.

The majority of patients with N_{2B} disease usually have a large node of N_{2A} equivalence plus other smaller lymph nodes located at other levels in the neck. Occasionally, lobular masses of metastatic lymph nodes which have become matted together through extracapsular extension are staged initially as a single lymph node, revealing their true multiplicity only at the end of the irradiation. The N_{2A} and N_{2B} stagings have been combined in the analysis because of the similarity of volumes of cancer.

The total dose delivered to a given lymph node or lymph nodes was determined by the original volume of nodal disease, the rate of its regression during treatment, and its anatomic relation to the treatment fields for the primary lesion. There has been a bias toward delivering higher doses over longer periods of time to larger volumes of disease. This concept has certainly influenced the dose levels given to the cervical lymph node metastases under study. It has been shown[6] that approximately 50 per cent of 2 to 3 cm. in diameter nodal disease is controlled by 5,000 rads external irradiation. In this series, the smaller volume of disease represented by the N_1 presentation was controlled in over 90 per cent of the patients at the level of 6,500 rads. Doses in excess of 6,500 rads do not increase control of N_1 disease since a plateau in the dose-response curve is reached.

A dose-response curve is not elicited for N_2 neck disease, which is to be expected in heterogeneous groups of tumors.[8] Doses of at least 6,500 rads up to 8,000 rads often were delivered to masses 5 to 10 cm. in diameter. Even with these doses, failures are to be expected.

When coverage and the irradiation dose are uncertain or there is a large volume of disease, control rates are lower and external irradiation should be supplemented by surgery. Other studies[1,7] have shown that fixed nodal metastases are more effectively treated by a combination of surgery and external radiation than by either modality alone.

CONCLUSIONS

1. The effectiveness of external radiation therapy to control cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts is determined by the volume of nodal disease.

2. When a single, nonfixed metastatic lymph node 3 cm. or less in greatest dimension is included well within the irradiated volume of the field for the primary lesion and receives approximately 6,500 rads, the control rate is excellent. If the single lymph node is not well within the irradiated volume, a neck dissection is indicated to assure control.

3. When a nonfixed metastatic lymph node of 3 cm. or more in greatest dimension or multiple lymph nodes are present, external irradiation alone cannot be relied upon for control and a neck dissection should follow.

SUMMARY

The records from 1948 through 1967 of 344 previously untreated patients with squamous cell carcinoma of the oral cavity, oropharynx, supraglottic larynx and hypopharynx who had clinically positive cervical lymph node metastases staged N_1, N_{2A}, or N_{2B}, and whose initial neck treatment consisted of external radiation therapy alone were reviewed.

After appropriate exclusions the study group consists of 183 patients. The dose to the lymph node(s) was calculated retrospectively. The control rates for N_1 lymph nodes are 91.5 per cent (76/83) and for N_2 lymph nodes 78.5 per cent (55/70) in the patients whose lymph node(s) were well included in the irradiated volume and received a known dose.

A dose response analysis shows that

doses in the range of 6,500 rads to a single lymph node, 3 cm. or less in diameter, produce 90 per cent control. When a nonfixed metastatic lymph node of 3 cm. or more in diameter or multiple lymph nodes are present or there is questionable coverage, external irradiation alone cannot be relied upon for control and a neck dissection should follow.

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AGGRESSIVE SURGERY IN TREATMENT FOR PAROTID CANCER: THE ROLE OF ADJUNCTIVE POSTOPERATIVE RADIOTHERAPY*

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ANALYSIS of long-term data revealing a significant incidence of recurrent cancer at the primary site has prompted a continuous search for improvement in treatment for parotid cancer. The intimate anatomic relation between the facial nerve and the parotid gland has been the most important factor influencing the various surgical procedures employed. Malignant cells were left at the primary site because the tumors were resected using either timid or anatomically unsound surgical approaches. Radiation therapy was equally disappointing in controlling the cancer, because of inadequate dose and poor field design. Radiation therapy was not universally used as an adjuvant to surgery, because cancer of the salivary glands acquired the reputation of being radioresistant. In recent years, as the surgical procedures were methodically perfected, the control rate improved.

The goals of this analysis are to determine whether an aggressive surgical program lessens the chance of local and regional recurrence and to assess the value of combining radiation therapy with the surgical procedure.

MATERIAL

The records of 120 previously untreated patients with malignant parotid tumors observed at the M. D. Anderson Hospital from 1944 through 1965 were analyzed. Seventy-nine (63 per cent) of the 120 patients had received prior surgical biopsy, but had not had definitive treatment. Excluded were patients with unresectable local lesions, those who refused treatment, and those with disseminated disease. Patients were eligible for a minimum 7 year to a maximum 28 year follow-up. A separate series of 29 patients receiving immediate postoperative radiation therapy was also studied. A few of these patients are also included in the series of 120 patients but most are not, either because they had a previous definitive surgical procedure before coming to our institution or they were treated since 1965. These patients are eligible for 4 year follow-up. Planned postoperative radiation therapy was rarely administered at M. D. Anderson Hospital before 1965.

CLASSIFICATION

The classification of salivary gland tumors based on histologic characteristics alone is not adequate to plan a program of treatment. To classify these neoplasms according to their biologic behavior and aggressiveness is equally, if not more,

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meaningful. Significant prognostic findings found at the surgical procedures included histologic evidence of invasion of nerves or perineural spaces, extension beyond the confines of the parotid gland, *i.e.*, invasion of the mandible, ear canal, temporal bone, masseter muscle, temporo-mandibular joint, skin, and presence of local or regional lymph node metastases.

We, therefore, divided these lesions into 2 groups. Comprising the "moderately malignant tumors" are the mucoepidermoid carcinomas of low grade, the acinic cell carcinomas and the well-differentiated adenocarcinomas. The highly malignant tumors include the mucoepidermoid carcinomas of high grade, malignant mixed tumors, adenocystic carcinomas, the more anaplastic adenocarcinomas, undifferentiated carcinomas and squamous cell carcinomas. The adenoid cystic carcinoma, or cylindroma, is included among the "highly malignant tumors" because of its remarkable tendency to infiltrate nerves and other structures, its frequency of local recurrence and its tendency to widely metastasize. Many authors have chosen to place the adenoid cystic lesion in an intermediate group of malignancy because short-term results are often quite good.[1,2] Long-term data reveal, however, that recurrence often appears much later than for most other parotid cancers.

TABLE I

PAROTID CANCER (1944–1965)
ABSOLUTE 5 YEAR SURVIVAL

(120 Patients)

	No. of Patients	5 Year Survival (Per Cent)
Acinic cell	12	92
Mucoepidermoid (low grade)	28	76
Adenocarcinoma	12	66
Malignant mixed	27	50
Adenoid cystic	10	50
Squamous cell	6	50
Mucoepidermoid (high grade)	13	46
Undifferentiated	12	33

RESULTS

The 5 year absolute survival of the patients according to the classification advocated by Foote and Frazell[4] is analyzed in Table I.

Control within the regional parotid and neck area was investigated in detail. The initial treatment, the number of local and regional treatment failures, subsequent treatment if employed and the number of patients whose second treatment did not produce another 5 year disease-free interval are shown in Tables II through VII. A few patients whose second treatment has produced a disease-free interval greater than 2, but less than 5 years are designated in the Tables. The facial nerve or one of its

TABLE II

MUCOEPIDERMOID (LOW GRADE) AND ACINIC CELL CARCINOMA

(40 Patients)

First Treatment	Failure	Second Treatment	Ultimate Local and Regional Failure
38 Surgery	3 (4 to 108 mo.)	Radiation	0
		Surgery	0
		Surgery and Radiation	1*
2 Surgery and Radiation	0		0

Resection of facial nerve—9 patients.

* Control <5 yr.

TABLE III

ADENOCARCINOMA

(12 Patients)

First Treatment	Failure	Second Treatment	<5 Yr. Ultimate Local and Regional Failure
10 Surgery	4 (3 to 24 mo.)	3 No Treatment	3
		1 Radiation	0
1 Radiation	1 (12 mo.)	Radical Radiations	1*
1 Surgery and Radiation	0		0

Resection of facial nerve—1 patient.

* Controlled <5 yr.

TABLE IV

MALIGNANT MIXED TUMOR

(27 Patients)

First Treatment	Failure	Second Treatment	Ultimate Local and Regional Failure
24 Surgery	5 (6 to 15 mo.)	1 No Treatment	1
		2 Surgery	1
		2 Radiation	1
2 Radiation	1 (9 mo.)	No Treatment	1
1 Surgery and Radiation	1 (16 mo.)	No Treatment	1

Resection of facial nerve—10 patients.

TABLE V

ADENOID CYSTIC CARCINOMA

(10 Patients)

First Treatment	Failure	Second Treatment	Ultimate Local and Regional Failure
8 Surgery	4 (1 to 4 yr.)	1 Surgery	1
		3 No Treatment	3
2 Surgery and Radiation	0		0

Resection of facial nerve—5 patients.

TABLE VI

MUCOEPIDERMOID (HIGH GRADE)

(13 Patients)

First Treatment	Failure	Second Treatment	Ultimate Local and Regional Failure
12 Surgery	3 (1 to 5 mo.)	2 No Treatment	2
		1 Surgery and Radiation	1*
1 Surgery and Radiation	0		0

* Controlled <5 yr.

major branches was resected in 22 per cent of the patients having tumors in the moderately malignant group and in 40 per cent of those having lesions of high-grade potential.

There is a definite relationship between local control of these tumors and the incidence of distant metastases (Table VIII). Those patients whose primary lesion is not controlled have more than double the chance of developing distant metastases.

Twenty-nine patients, most of whom are not in this series of 120 patients, were given immediate postoperative irradiation and are analyzed separately (Table IX). Fifteen of these patients were known to have residual cancer in the surgical bed, while 14 patients were thought to have cancer remaining even though it might have been microscopic. All have been followed 4 years and over. To date, 4 (14 per cent) of the 29 patients have had local recurrence at 21, 23, 44, and 64 months. These 4 patients, all but one having high-grade tumors, were in the group of 15 patients known to have residual cancer; none were in the subclinical disease category.

These figures are superior to the 3 year recurrence of 73 per cent for highly malignant lesions reported by Beahrs *et al.*,[1] and the 26 per cent local and regional failure rate in this present surgical series.

DISCUSSION

The experience in this series dictates the necessity of improving the results of treatment which, until now, has been largely surgical. It also dispels the theory of the

TABLE VII

SQUAMOUS CELL CARCINOMA AND UNDIFFERENTIATED CARCINOMA

(18 Patients)

First Treatment	Failure	Second Treatment	Ultimate Local and Regional Failure
12 Surgery	7 (1 to 24 mo.)	5 No Treatment	5
		2 Radiation	2*
3 Radiation	1 (10 mo.)	1 No Treatment	1
3 Surgical and Radiation	1 (1 mo.)	1 No Treatment	1
7th nerve resection—11 patients.			

* Controlled <5 yr.

radioresistance of small aggregates of tumor or subclinical numbers of salivary gland cancer cells. Surgical operation is adequate therapy for the patients with moderately malignant lesions. Substantial evidence suggests that combining radiation therapy with the surgical procedure will reduce the incidence of local and regional tumor recurrences when treating the aggressive, high-grade cancers.[3]

Based on the data reported here, a rational plan of treatment for parotid cancer evolves. The minimal surgical procedure is a superficial parotidectomy with excision of the parotid and subdigastric lymph nodes. An exact evaluation of the extent and aggressiveness of the cancer must be ascertained. If frozen section histology indicates that the lesion is low grade and not locally aggressive, parotidectomy will be sufficient. Parotidectomy is also adequate for small, selected high-grade lesions which can be resected with wide margins. If the lesion is in the high-grade group and extensive spread of cancer is observed at the time of the surgical procedure, the deep lobe, facial and auriculo-temporal nerves, muscle, bone and skin, as indicated, should also be removed in a meticulous effort to eliminate all gross tumor. Any areas of unresectable gross cancer or suspected microscopic disease must be noted for future radiation therapy. The first echelon of parotid and subdigastric lymph nodes are also removed. If these are positive, a radical neck dissection is performed; if negative, neck dissection is not necessary.

The surgical bed and entire surgical scar of all patients with high-grade and locally aggressive lesions are irradiated as soon as healing is complete to a midline tumor dose of 5,000 rads in 5 weeks if only subclinical cancer is suspected. An additional 1,000 to 1,500 rads in 5 to 7 treatments is given known areas of gross disease through reduced portals[3] (Table x). Postoperative therapy fields are highly individualized according to the findings during the sur-

Table VIII

PAROTID CANCER
DISTANT METASTASIS
(18 of 120 Patients)

	Distant Metastasis With Local Control	Distant Metastasis Without Local Control
Mucoepidermoid	1	1
Malignant mixed	3	2
Adenoid cystic	1	2
Adenocarcinoma	—	3
Undifferentiated	—	3
Acinic cell	—	1
Squamous cell	—	1
Total	5	13

Table IX

MALIGNANT SALIVARY GLAND TUMORS
PATIENTS TREATED POSTOPERATIVELY
(Local Failure by Histology: 4 yr. to Unlimited Follow-up)

Histology	No. of Patients	No. of Recurrences
Malignant mixed	3	2*
Mucoepidermoid (high grade)	7	0
Adenocystic	8	1*
Adenocarcinoma	4	0
Acinic cell carcinoma	1	0
Squamous cell carcinoma	4	1*
Undifferentiated carcinoma	1	0
Unclassified neoplasm	1	0
Total	29	4 (14%)

* Recurrences at 21, 23, 44, and 64 months. All had definite postexcisional residual disease.

Table X

PAROTID CANCER
INDICATIONS FOR POSTOPERATIVE IRRADIATION

1. Highly malignant tumors
2. Invasion of muscle, bone, skin, temporo-mandibular joint, nerves or perineural lymphatics
3. Regional lymph node metastases
4. After resection of recurrent tumor
5. Tumors of the deep lobe
6. Gross residual tumor after surgical resection
7. The tumor is adjacent to facial nerve

gical procedure. The minimal fields extend from the superior edge of the zygoma above and extend below the mandible and cover the subdigastric lymph nodes below. The minimal anterior border is the anterior edge of the masseter and the minimal posterior field covers the posterior edge of the parotid. If the facial nerve is involved, or the patient has an adenoid cystic cancer, the mastoid bone must be irradiated; if the auriculo-temporal nerve is involved, the radiation must be delivered to the base of the skull. The entire ipsilateral side of the neck is often included in the radiation field of patients with the most undifferentiated tumors, even if the neck is clinically negative; the ipsilateral side of the neck is given 5,000 rads in 4 weeks, preferably with an electron beam. If positive lymph nodes were present at the surgical procedure, the same fields are used, but the neck receives postoperatively 6,000 rads in 6 weeks.

A policy of handling the facial nerve which varies from the traditional is suggested by these data. All or a portion of the nerve should be resected back to clear margins, if the nerve has gross cancer in it. If the tumor is found adjacent to but not invading the facial nerve, it may be cleaned off and the nerve spared in favor of giving postoperative radiation therapy, even though the classic concepts of adequate margins of tissue free of tumor would dictate removal of the nerve. Important function is preserved without compromising the patient's chances of cure.

SUMMARY

A 7 year follow-up of 120 patients with malignant parotid cancers reveals parotidectomy to be an adequate procedure for low-grade, nonaggressive lesions.

The addition of radiation therapy postoperatively will improve local and regional control of high-grade, aggressive lesions. Postoperative radiation therapy may also make the removal of the facial nerve unnecessary in certain clinical presentations.

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HYPERURICEMIA IN CANCER OF THE LARYNX*

PRELIMINARY REPORT

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ELEVATED serum uric acid is known to occur in some adult patients with gout, leukemia and lymphoma, in patients with polycythemia vera, multiple myeloma, in patients with toxemia of pregnancy and in those with chronic glomerulonephritis.[1] In children the serum uric acid has been reported as being increased in patients with reticulum cell sarcoma, leukemia, rhabdomyosarcoma, lymphosarcoma, Wilms' tumor, neuroblastoma, and Ewing's sarcoma.[3] Hyperuricemia has also been recorded in patients with disseminated carcinomas (carcinoma of breast, lung, digestive tract, prostate, thyroid, melanoma, osteosarcoma, hypernephroma).[6] More recently cases with hyperuricemia have been found in cancer patients following antitumor treatment (chemotherapy and irradiation).

The purpose of this paper is to record the serum uric acid values in a series of 94 cancer patients. All of the cases were treated with supervoltage irradiation (cobalt 60 or 2 mev), some with combined surgery, x-ray and chemotherapy. These patients were treated for palliation or cure depending on the extent of involvement (staging). A small percentage of all cases had disseminated disease.

Analysis of this series of cases strikingly records a persistent hyperuricemia in the patients with carcinoma of the larynx. The serum uric acid levels for all of the other cancers were nonspecific.

METHOD OF EVALUATION

The approach in the evaluation of the serum uric acid level in our cancer patients was to take a blood uric acid value prior to irradiation on all of the pathologically proven cancer patients, and to repeat the tests on a weekly basis up to the time of completion of the irradiation. All of the patients had routine physical examinations and appropriate laboratory work-up. None were known to have any related renal disease. The patients were not selected and no controlled study was made. All patients were treated with Co^{60} or 2 mev irradiation, with average daily doses of 200 rads.

RESULTS

The normal serum uric acid value for our hospital is 3–6 mg./100 ml. Blood uric acid levels above 6 are considered abnormal. Table 1 lists the patients by age, sex, diagnosis, radiation dose, and serum uric acid levels from initial treatment to last recorded uric acid value taken upon completion of irradiation.

DISCUSSION

Uric acid represents the end product of purine metabolism and is the result of breakdown of nucleic acid. In the normal individual it is found in the blood serum and urine in average amounts 3.5 mg./100 ml. serum and 450 mg./24 hr. in urine, respectively. With a high metabolism the serum and urine uric acid rises in some individuals. Diet will also affect the serum uric level.

With malignancy (leukemia and lymphoma) a rapid breakdown of the malignant cells accounts for the elevated uric acid. This is known to occur especially after chemotherapy and irradiation. Elevated serum uric acid is also recorded as occurring with disseminated carcinomatosis with variable values for the different carcinomas and for each individual case. Excepting for our patients with carcinoma of

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TABLE I

SUMMARY OF PATIENTS

	Name	Age	Sex	Diagnosis	Dose (rads)	Uric Acid (mg./100 ml.)
1.	S.L.	60	M	Ca lung	4,600	4.6→5.1
2.	L.C.	68	F	Ca lung	4,000	3.5→4.0
3.	W.R.	72	F	Ca lung	3,000	4.5→6.1
4.	E.F.	64	F	Ca lung	4,200	3.4
5.	B.R.	68	M	Ca lung	4,000	6.5
6.	C.F.	63	F	Ca lung	4,200	3.4→4.3
7.	W.D.	54	M	Ca lung	4,000	5.6
8.	T.C.	62	M	Ca lung	5,000	5.7→3.9
9.	T.H.	61	M	Ca lung	4,000	6.5→6.2
10.	M.L.	74	M	Ca lung	4,600	3.1→2.3
11.	W.R.	72	M	Ca lung	4,000	4.5→6.1
12.	H.B.	65	M	Ca lung	5,000	3.5→2.2
13.	P.C.	87	M	Ca lung	4,000	4.9→4.4
14.	G.J.	68	M	Ca lung	3,000	3.7→3.5
15.	L.R.	64	M	Ca lung	4,000	3.8→4.4
16.	W.B.	60	F	Ca lung	3,600	4.4→3.6
17.	H.D.	66	M	Ca lung	4,000	3.7→4.0
18.	L.R.	44	M	Ca lung	3,900	4.2→4.8
19.	J.E.	73	M	Ca lung	4,000	3.1→3.6
20.	W.R.	72	F	Ca lung	2,400	4.6→6.1
21.	M.H.	74	F	Ca breast	3,000 spine	3.7→5.8
22.	D.L.	70	F	Ca breast	5,000	4.7→4.6
23.	D.J.	68	F	Ca breast	5,000	2.4→2.1
24.	A.E.	51	F	Ca breast	5,000	4.9→4.8
25.	C.J.A.	50	F	Ca breast	5,000	5.1→4.9
26.	S.E.	73	F	Ca breast	5,000	4.3→3.7
27.	H.A.	48	F	Ca breast	5,000	6.9→7.2
28.	P.S.	59	F	Ca breast	5,000	5.6→5.4
29.	C.D.	40	F	Ca breast	5,000	2.0→1.8
30.	D.O.	25	F	Ca breast	5,000	4.4→4.4
31.	R.N.	39	F	Ca breast	2,500 bone	3.9→4.6
32.	W.R.	57	F	Ca breast	4,500	4.4→3.8
33.	R.W.	43	F	Ca breast	4,500	3.8→3.7
34.	R.E.	57	F	Ca breast	4,500	3.9→3.7
35.	I.L.	50	F	Ca breast	4,500	4.1→4.6
36.	G.C.	45	F	Ca breast	4,500	5.3→4.2
37.	C.R.	81	F	Ca cervix	4,000+radium	4.3→3.7
38.	B.P.	35	F	Ca cervix	4,000+radium	5.5→3.5
39.	R.M.	60	F	Ca cervix	4,000+radium	3.7→3.4
40.	G.J.	82	F	Ca cervix	4,000+radium	3.5→2.9
41.	A.E.	31	F	Ca cervix	4,000+radium	2.8→3.2
42.	H.A.	44	F	Ca cervix	4,000+radium	2.8→4.1
43.	R.P.	33	F	Ca cervix	4,000+radium	4.2→4.8
44.	H.L.	38	F	Ca cervix	4,000+radium	4.8→3.6
45.	P.A.	60	F	Ca cervix	4,000+radium	4.0→4.4
46.	S.A.	61	F	Ca cervix	4,000+radium	3.6→4.0
47.	G.G.	63	F	Ca cervix	4,000+radium	6.0→5.1
48.	R.V.	44	F	Ca cervix	4,000+radium	3.2→3.4
49.	G.D.	55	F	Ca cervix	4,000+radium	3.7→3.5
50.	R.M.	29	F	Ovarian Ca	4,000	3.7→3.4
51.	S.R.	40	F	Ovarian Ca	4,000	3.0

Ca = Carcinoma.

TABLE I (continued)

SUMMARY OF PATIENTS

	Name	Age	Sex	Diagnosis	Dose (rads)	Uric Acid (mg./100 ml.)
52.	G.L.	29	F	Ovarian Ca	4,000	3.2→4.3
53.	B.L.	71	F	Ovarian Ca	4,000	8.2→8.9
54.	O.I.	50	F	GU Gartner's duct	5,000	1.8→2.2
55.	M.G.	60	M	Bladder	5,000	3.9→2.7
56.	M.R.	55	M	Prostate	2,000	1.8→2.8
57.	C.H.	62	M	Prostate	3,000	4.9→5.5
58.	S.S.	16	M	Ca kidney	3,700	5.3→6.6
59.	C.G.	46	F	Ca bladder	4,900	3.3→4.4
60.	S.F.	62	F	Nasopharynx	2,900 bone	2.7→2.9
61.	G.E.	60	F	Pharynx	4,000	3.6→4.3
62.	S.L.	56	F	Tonsillar pillar	6,000	6.5→6.4
63.	W.H.	68	M	Base tongue	6,000	5.7→3.8
64.	D.J.	64	M	Tonsil	6,000	5.7→5.0
65.	K.L.	57	M	Lips	4,800	5.9
66.	S.A.	77	M	Maxillary sinus	6,000	3.9→4.4
67.	G.E.	68	M	Esophagus	6,000	4.8→3.5
68.	S.K.	66	M	Esophagus	3,800	1.5→1.7
69.	T.G.	72	M	Ca rectum	4,000	7.8→7.6
70.	R.J.	74	M	Larynx	2,000	4.4→5.7
71.	G.M.	64	M	Larynx	4,000	9.3→10.2
72.	M.G.	51	M	Larynx	6,000	10.6→10.6
73	G.E.	65	M	Larynx	4,000	5.7→7.6
74.	L.G.	49	M	Larynx	6,000	6.6→6.1
75.	H.R.	61	M	Larynx	6,000	5.4→6.3, 5.4
76.	D.J.	63	M	Larynx	4,000	5.6→6.2
77.	B.	64	M	Larynx	6,000	8.8→9.7
78.	O.C.	70	M	Pharynx	5,400	5.5→5.7
79.	P.W.	56	M	Brain tumors	4,000	2.6→2.6
80.	K.L.	43	F	Brain tumors	4,000	2.1→3.1
81.	A.M.	24	F	Brain tumors	5,400	4.9→4.0
82.	T.D.	13	F	Brain tumors	2,000	3.7→3.4
83.	P.H.	50	M	Brain tumors	4,000	3.0→2.7
84.	A.A.	42	F	Brain tumors	4,850	6.0→6.5
85.	G.L.	2	M	Brain tumors	800	4.6→3.3
86.	C.L.	55	F	Brain tumors	4,500	3.9→4.2
87.	K.S.	46	F	Brain tumors	2,000	4.0→5.0
88.	L.T.	41	M	Brain tumors	4,000	4.1→3.3
89.	G.P.	55	M	Lymphoma	4,000	5.9→6.7
90.	A.M.	63	M	Lymphoma	3,000	3.7
91.	H.A.	31	M	Lymphoma	4,000	4.2→4.8
92.	L.M.	50?	M	Lymphoma	4,000	3.8→4.0
93.	S.C.	57	M	Lymphoma	4,000	4.4→4.2
94.	O.C.	66	F	Ca spine, metastasis	3,000	4.6→4.5

the larynx, hyperuricemia is seen only in a few scattered cases for all of the malignancies.

In our series a persistent hyperuricemia was found only in the patients with carcinoma of the larynx. All of these had primary carcinoma of the larynx, some with and others without regional lymph node involvement. The explanation for increased serum uric acid in carcinoma of the larynx is difficult. An increased, rapid cell (nucleic acid) destruction can account for the

TABLE II

CARCINOMA OF THE LARYNX

Case		Diagnosis	Stage	Irradiation Therapy (rads)	Unit	Serum Uric Acid (mg./100 ml.)
1.	R.I.	Sq. Cell Ca Epiglottis	III	Chemotherapy and Irradiation 7,000	Co^{60}	4.4→ 5.7
2.	G.M.	Sq. Cell Ca Transglottic	III	Irradiation 6,000	2 MEV-Co^{60}	9.3→10.2
3.	M.G.	Sq. Cell Ca True Cord and Subglottic	III	Post-Laryngectomy 6,000	Co^{60}	10.6→10.6
4.	G.E.	Sq. Cell Ca Transglottic	IV	Surg.-Chemotherapy and Irradiation 6,000	Co^{60}	5.7→ 7.6
5.	L.G.	Sq. Cell Ca Epiglottis	III	Chemotherapy and Irradiation 7,000	Co^{60}	6.6→ 6.1
6.	H.R.	Sq. Cell True Cord	I	Irradiation 6,000	2 MEV	5.4→ 6.3, 5.4
7.	D.J.	Sq. Cell Epiglottis and True Cord	II	Surgery and Irradiation 4,000	2 MEV	5.6→ 6.2
8.	B.T.	Sq. Cell Supra- and Infraglottic	II	Irradiation and Surgery 6,000	Co^{60}	8.8→ 9.7

Sq. Cell Ca = squamous cell carcinoma.

elevated serum uric acid in those with true glottic squamous cell carcinoma. This in part may be due to its high sensitivity to radiation or chemotherapy.

The larynx consists of cartilage, muscle, connective tissue, and mucous membrane lining of columnar epithelium cells. The thyroid and cricoid cartilages constitute the basic framework of the larynx which is supported by intrinsic and extrinsic muscles and ligaments surrounded by blood and lymphatic vessels. The true cords, attached to perichondrium of the thyroid cartilage, have a poor lymphatic drainage. The supraglottic (epiglottis) and infraglottic structures, the laryngeal ventricle, and aryepiglottic folds have a rich lymphatic supply—known as the extrinsic larynx (all parts of larynx except true cords and anterior commissure). For this area (extrinsic larynx) cervical lymphadenopathy is common.[5]

Treated with irradiation alone, or combined with surgery and/or chemotherapy, 7 of 8 of the laryngeal carcinoma cases had an increased serum uric acid. The eighth case had a borderline elevated serum uric acid.

Generally, hyperuricemia in cancer patients is considered as a complication which requires treatment, since it can lead to acute nephropathy.[4] Associated symptoms

TABLE III

SUMMARY OF ALL CASES—SERUM URIC ACID

	Abnormal* Uric Acid ↑ (Increased)	Post-Irradiation† Value		Total Cases
		↑ (Increased)	↓ (Decreased)	
Lungs	5	10	7	20
Breast	1	4	11	16
Cervix	1	6	7	13
Ovary	1	2	1	4
Genitourinary	1	5	1	6
Oral-pharynx	1	3	3	8
Lymphoma	2	3	1	5
Brain	1	4	5	10
Gastrointestinal	0	1	2	3
Miscellaneous	0		1	1
Larynx	7	5	1	8
Totals	20	43	40	94

* Abnormal value serum uric acid above 6 mg./100 ml.
† No change or only 1 value obtained for 11 cases.

are anorexia, vomiting, hematuria, oliguria, or anuria.

There were no positive clinical symptoms of hyperuricemia in any of our cases. The patients were on a regular diet and no uricosuric drugs were administered to the patients (aspirin, chlorothiazide, corticosteroids).

Hyperuricemia was found prior to irradiation in the majority of the cases and in most of the cases there was no convincing evidence of increased serum uric acid after irradiation. (In 43 cases the serum uric acid was elevated and it was decreased in 40 cases; 11 had no change or had only 1 serum value performed.)

Significantly the serum uric acid was abnormal above 6 mg./100 ml., consistent with hyperuricemia in 7 of 8 carcinomas of the larynx, abnormal in 5 of 20 lung cancers, in 2 of 5 lymphomas, and as single abnormal values for each of the other carcinoma groups.

CONCLUSION AND SUMMARY

Serum uric acid values were obtained in 94 patients with cancer, prior to and upon completion of radiation therapy. Hyperuricemia was persistent in all of the patients with carcinoma of the larynx. Explanation for this finding is uncertain. Serum uric acid levels for all other cancers, in this series, were not impressive.

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COMPUTER-ASSISTED THYROIDAL TECHNETIUM UPTAKE MEASUREMENT USING A SHORT PINHOLE-TO-SURFACE DISTANCE

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IN recent years many laboratories have begun using the early thyroidal uptake of Tc-99m pertechnetate as an indication of the trapping ability of the thyroid and as a useful guide to its general functioning state. Good correlation with clinical state compared with the traditional later (*e.g.*, 24 hour) I-131 uptake has been reported.[3,8]

In this hospital, a 10 minute uptake has been used routinely to give anatomic information and assist, together with biochemical tests, in the assessment of thyroid function. Over a period of 3 years 780 subjects have been scanned, the majority of whom presented with suspected hyperthyroidism. The upper limit of normal uptake has been determined as 2.0 per cent of administered dose.

Although the early uptake presents a number of technical problems when compared to the later uptake, if a combined gamma camera-computer system is available most of these may be overcome.

Such camera-computer systems have been described in the literature in recent years.[2,6,8,10] Some of these papers have also discussed at length the problems met in this type of study, which may be briefly summarized as follows:

1. The background, or extrathyroidal neck radiation (ENR), is usually of the same order of magnitude as the thyroid uptake.

2. Thyroid tissue must be delineated from adjacent organs which concentrate pertechnetate (and from ENR).

3. Commonly the uptake values are low compared to iodine uptakes.

4. The time of the maximum uptake is unpredictable (although no more so than for iodine uptakes).

5. Most gamma cameras have nonuniform response to radiation across their detector area, and this is especially significant if a pinhole collimator is used.[1,2,4]

6. The self-absorption of technetium gamma rays within the gland and overlying tissue is much more significant than for I-131.

In most published reports, a pinhole collimator is used due to the magnification and increased resolution it affords for thyroid studies.[9] If such a collimator is used, many of the problems summarized above are to some extent functions of the distance of the pinhole from the anterior surface of the neck (relative to the pinhole-to-crystal distance), which will be henceforth referred to as the *viewing distance*. If the viewing distance is large compared to thyroid dimensions, the whole gland will always be viewed, the effects of camera nonuniformity due to the collimator will be small—as long as the thyroid is reasonably central in the field of view, and errors due to different viewing distances from patient to patient (and to the standard) will be negligible.

The disadvantages, however, are that camera sensitivity will be very low, severely limiting the statistical reliability of dynamic studies and increasing static imaging time, and methods for excluding other pertechnetate-accumulating organs (*e.g.*, salivary glands) within the field of view during uptake calculation will be necessary. Scan resolution will also be suboptimal.

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METHOD

In the Nuclear Medicine Department at this hospital, a Nuclear Enterprises Scinticamera III camera and PDP 8/I computer with 8k of memory are used, and the viewing distance is 7 cm. The patient lies supine with his head hyperextended with a soft support under the neck to enable the throat to be kept horizontal, and the viewing distance is carefully fixed using an appropriate perspex spacer. Experience has shown that at this distance the salivary glands are very rarely seen in the scintiphoto, and yet the whole of the thyroid is almost always visualized. (Subsequent scintiphotos at 12 cm. distance, routinely taken on each patient for localization purposes, have always shown this to be true.)

The advantages of this method are:

1. Scan resolution is excellent.
2. Subject to adequate allowance for ENR, discussed below, no involved processing of the scan to delineate the gland is needed.
3. Sensitivity is comparatively high, and computer-recorded "frames" may be taken at the rate of 15 per minute (or faster) with excellent statistics. The advantages of this for research are obvious, and we are currently using this feature to examine the very early uptake (*i.e.*, from 0 to 3 minutes after injection) of the thyroid to pertechnetate and other radionuclides. Furthermore, even in a busy department concerned only with routine scans and single uptake measurements, a significant saving in scanning time is obtained.

PROBLEMS IN TECHNIQUE

There are some problems which are magnified with use of a short viewing distance. These may be dealt with in the following ways.

1. NONUNIFORMITY IN CAMERA SENSITIVITY

The nonuniformity of camera response due to the use of the pinhole collimator causes a considerable decrease in sensitivity away from the center of the scintiphoto for large thyroids, whereas the reference standard (in this case, a 3 cm. external diameter cylindrical bottle of pertechnetate in an IAEA standard neck phantom) is always held near the center of the view. Insofar as computer calculations are concerned, this problem, together with that of the inherent nonuniformity of a gamma camera to a uniform plane source of activity, is easily eliminated by the use of correction methods described by other workers.[2,10] A matrix of correction factors, normalized to some reference point, and based on the viewing of a thin sheet of activity placed perpendicular to the viewing axis through the same collimator at the same viewing distance, is stored in the computer memory, and these are applied to each point in the 32×32 image frame matrix—a process which can be accomplished in a few seconds.

2. GEOMETRIC VARIATIONS

At this viewing distance, compared to greater viewing distances, the effects of the inverse square law on sensitivity are more significant.[2,8] Calculations show that an error in the setting up of this distance of ± 3 mm. (which may be introduced if, for example, the surface of the neck is not perpendicular to the pinhole axis) gives a sensitivity error of ± 8 per cent. It has been stated above that considerable care is taken to ensure correct distance; random checks by the authors of scan positions set up by operating technicians have shown that this is a reasonable maximum error range. Also a number of repeat scans separated by a day or so have all yielded result of reproducibility well within this range.

Furthermore, the gland and neck geometry will affect the effective detector sensitivity, and hence the measured uptake, because of variations in the size and position of the patient's thyroid, for a constant viewing distance. This source of error arises partly from photon absorption within the gland and neck (which factor is of course common to all external methods of measuring uptake), and partly from inverse square law effects, when different

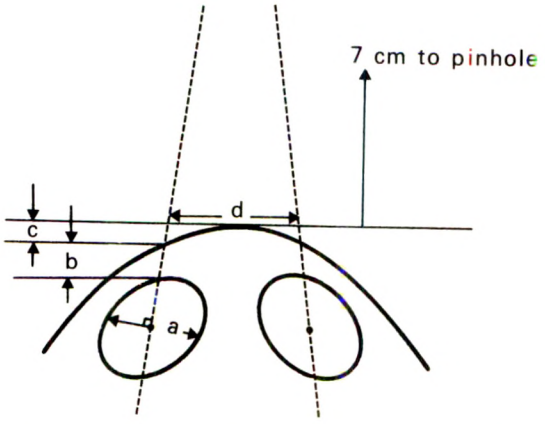

FIG. 1. A representative transverse section of the neck and thyroid lobes, demonstrating the geometric parameters described in the text.

parts of the thyroid are at different distances from the pinhole. The various geometric parameters involved are shown in Figure 1; they amount in practice to the following:

(i) measures of the size and shape of the thyroid (*e.g.*, *a* in Fig. 1), and of the separation (*d*) of the thyroid lobes;

(ii) a measure of the curvature of the patient's neck over the thyroid (*e.g.*, *c* in Fig. 1); and

(iii) a measure of the average depth of nonthyroidal tissue overlying the thyroid (*b*).

Each of these factors is discussed more fully below.

Theoretical calculations were made of the effect on sensitivity of varying the shape of a thyroid lobe, treating the lobe as an ellipsoid with various major and minor axes, and taking into account both inverse square law and absorption effects. The results of these calculations are presented graphically in Figure 2, and this indicates that the variation in sensitivity (for a neck of constant curvature and thyroid depth) is about ±20 per cent, as the apparent cross-section, as "seen" by the pinhole, varies from a circle to an ellipse (either prolate or oblate) with a ratio of axes of 2:1. This variation in sensitivity represents extremes in practice; in fact the apparent cross-section tends to be approximately circular, in consequence of the fortuitous angulation of the long axis of most thyroid lobes (which happens to be at about 45° to the line joining the center of the lobe to the pinhole—see Fig. 1). Thus the variation in sensitivity due to gland shape is unlikely in practice to exceed ±10 per cent.

The correction factors routinely applied in this department to compensate for different patient neck sizes and gland sizes are combined into a single set of graphs, based on the results depicted in Figure 3. The primary effect of variations in neck curvature is to vary the actual distance of the thyroid gland from the pinhole (for a

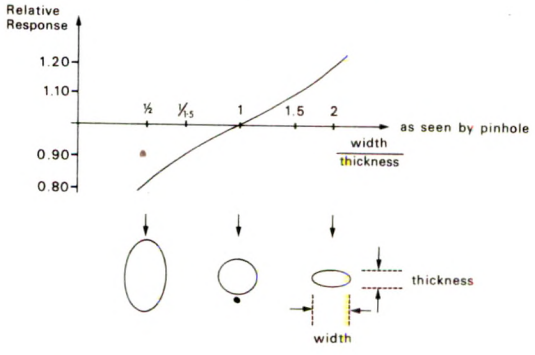

FIG. 2. Relative sensitivity of the pinhole-collimated camera for ellipsoid volumes of activity. The "depth" of the lobe is varied while the apparent width, as viewed from above, is constant.

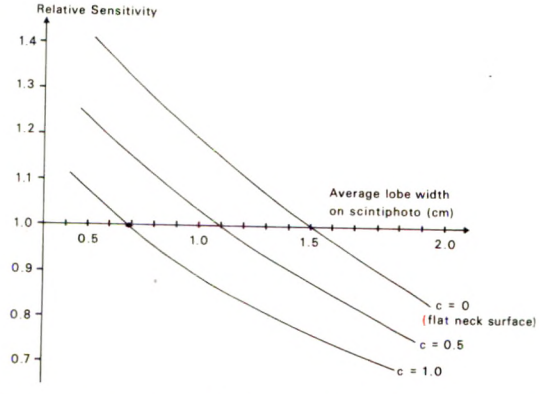

FIG. 3. Relative sensitivity of the pinhole-collimated camera for variable neck curvature (*c*) and lobe width (as seen on the scintiphoto). Lines for intermediate values of *c* have been deleted from this version to avoid cluttering.

constant viewing distance). If (as has been ascertained from a large number of scans) the interlobe distance (*d* in Fig. 1) is relatively constant, the neck curvature is determined to a first approximation by the distance *c* in Figure 1. This distance can easily be determined for each patient to the nearest millimeter by matching his neck curvature over the thyroid to the appropriate one of a set of templates.

In addition it proved possible to estimate both theoretically and experimentally the results of both inverse square law and absorption effects when the thyroid lobe size varies, and the analysis of both curvature and size factors yielded the curves of Figure 3. These give the relative sensitivity of the detector at the standard viewing distance as a function of the lobe diameter (as measured on the scintiphoto) for different neck curvatures. The theoretical determinations were made (as were those for Fig. 2) by integrating the contributions "point sources" at different points within ellipsoid-shaped "glands" embedded in an absorbing medium of unit density; these were verified experimentally (for the case of cylindrical lobes) by measurements using cylindrical bottles of different diameters and lengths but containing the same amount of activity.

In practice the curves of Figure 3 are simple to use. The correction factor rarely exceeds ±10 per cent, since large glands (*e.g.*, one with a size measured on the scintiphoto of about 1.5 cm.) tend to occur (or to produce) large necks with curvature *c* close to zero, whereas normally sized glands (measured diameter of 7–10 mm.) have a curvature *c* of 5 cm. or greater; in either case the "relative sensitivity" is indicated by Figure 3 to be close to 1.0. However, the number of exceptions to this trend is sufficient to justify the continued use of this correction factor.

Variation of the depth of tissue overlying the thyroid is much harder to compensate for, and indeed it was found to be impractical to assess this depth with sufficient accuracy by available methods, such as the performance of lateral views of a patient's neck. Our tentative results tend to support the view of Hurley *et al.*[8] that this depth (*b* in Fig. 1) is fairly constant and roughly 5 mm. This value has been assumed in our calculations and measurements. However, our further investigations to estimate the significance of this variable on the uptake determination will employ ultrasonic beta-scanning techniques.

3. ENR SUBTRACTION

With the relatively close viewing distance, the assessment of ENR for subtraction purposes becomes difficult when imaging large thyroids (which may almost fill the viewed area) or poorly visualized glands, in which case discrimination between thyroid and nonthyroid tissue becomes a subjective choice of the operator. In both situations there may be insufficient background areas available to make the usual method described by most workers accurate.[2,5,7,8,10] In other words, a representative ENR count cannot be found as a basis for subtraction from the thyroid area or image.

It was decided to investigate the amounts and distributions of ENR in a group of scans in which these problems were not present; *i.e.*, in which the thyroid area could be clearly differentiated on the image, and occupied less than half of the viewed area. In this group, the counts were measured in a rectangle of width equal to the thyroid width and length 1–2 cm., either superior or inferior to the thyroid (or both if possible).

In 61 scans the area above the thyroid had a value of 2.95 ± 0.75 counts/matrix location/millicurie dose (for this camera-computer system), with the error given as 1 standard deviation, and in 51 scans the area below the thyroid had 3.55 ± 0.95 counts/location/millicurie dose. It was seen that in each case values increased with thyroid uptake (this being the major contribution to the width of the error ranges), indicating that wide-angle scatter from the thyroid was being included. The exclusion

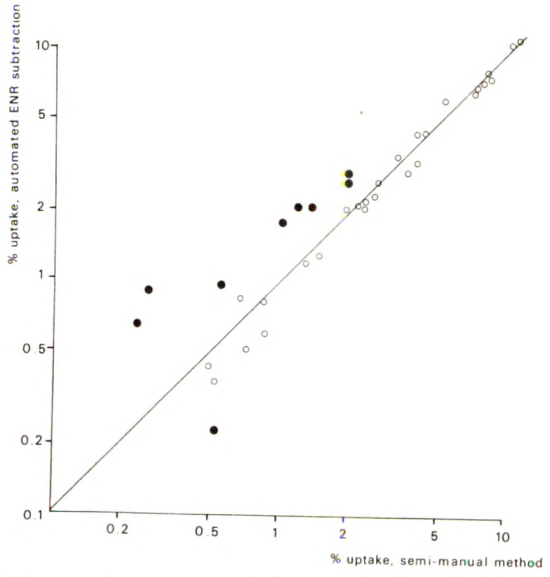

FIG. 4. Comparison of the semi-manual and automatic methods for calculating percentage uptake, for a series of 36 patients. Filled circles represent those patients for whom the results were significantly different. The upper limit of the normal range = 2.0 per cent.

of wide-angle scatter from ENR is allowable if the standard, counted under identical geometric conditions, is similarly counted; *i.e.*, if all counts (except room background) are included in the counting of the standard.

Scans were also carried out on 4 athyroid subjects (who had in the past had a total thyroidectomy followed by radioiodine), and counts taken over the region showed:

(a) the average ENR at the normal thyroid position = 3.0 counts/location/millicurie dose (range: 2.4–3.6); and

(b) in 3 of the subjects, a continuous decrease in ENR from the thoracic region upwards, which is probably due to the greater scattering volume and general vascularity in the upper thoracic region.

These results suggested that under these scanning conditions it is reasonable (empirically at least) to assume that the general population will have an ENR of 3 ± 1 counts/location/millicurie dose. Consequently, a simple computer program was written to perform routinely this ENR subtraction (see Appendix 1).

The thyroid Tc-99m uptakes of a group of 36 subjects were analyzed using both this method ("automated ENR subtraction") and the previously-used common "semi-manual" method (whereby areas of interest are chosen by the operator, computer output of counts in these areas obtained, and manual subtraction carried out). The results of their comparison are shown in Figure 4. In cases where agreement was not good, the scans were re-examined and it was found that in all cases except 1 the discrepancy was probably due to the inability of the operator, in the semi-manual method, to delineate accurately thyroid from nonthyroid tissue; *i.e.*, in visually poorly differentiated glands with low uptakes. In the case of the single exception, the background area chosen by the operator was wider than the thyroid area width and so the counts per location manually calculated gave an average ENR lower than it should have been.

SUMMARY

The close pinhole view of the thyroid presents some important measurement problems. Possible errors due to gland, neck and set-up geometry are accentuated due to the effects of the inverse square law, and care is needed to control these. The nonuniform response inherent in the use of the pinhole collimator has a significant effect, but with computer processing this is readily eliminated. ENR subtraction may become difficult in certain circumstances, as insufficient "background areas" may be viewed, but it has been shown that the use of a "universal" (for the particular system) ENR subtraction may give, if anything, more accurate results.

With these precautions in use, important errors will be of the same order of magnitude as those involved in more distant views, and may thus be kept within the realms of clinical significance.

On the other hand, considerable improvements in both resolution and sensitivity make the use of the closer view an asset to both the research laboratory and the small department involved mainly in routine service work.

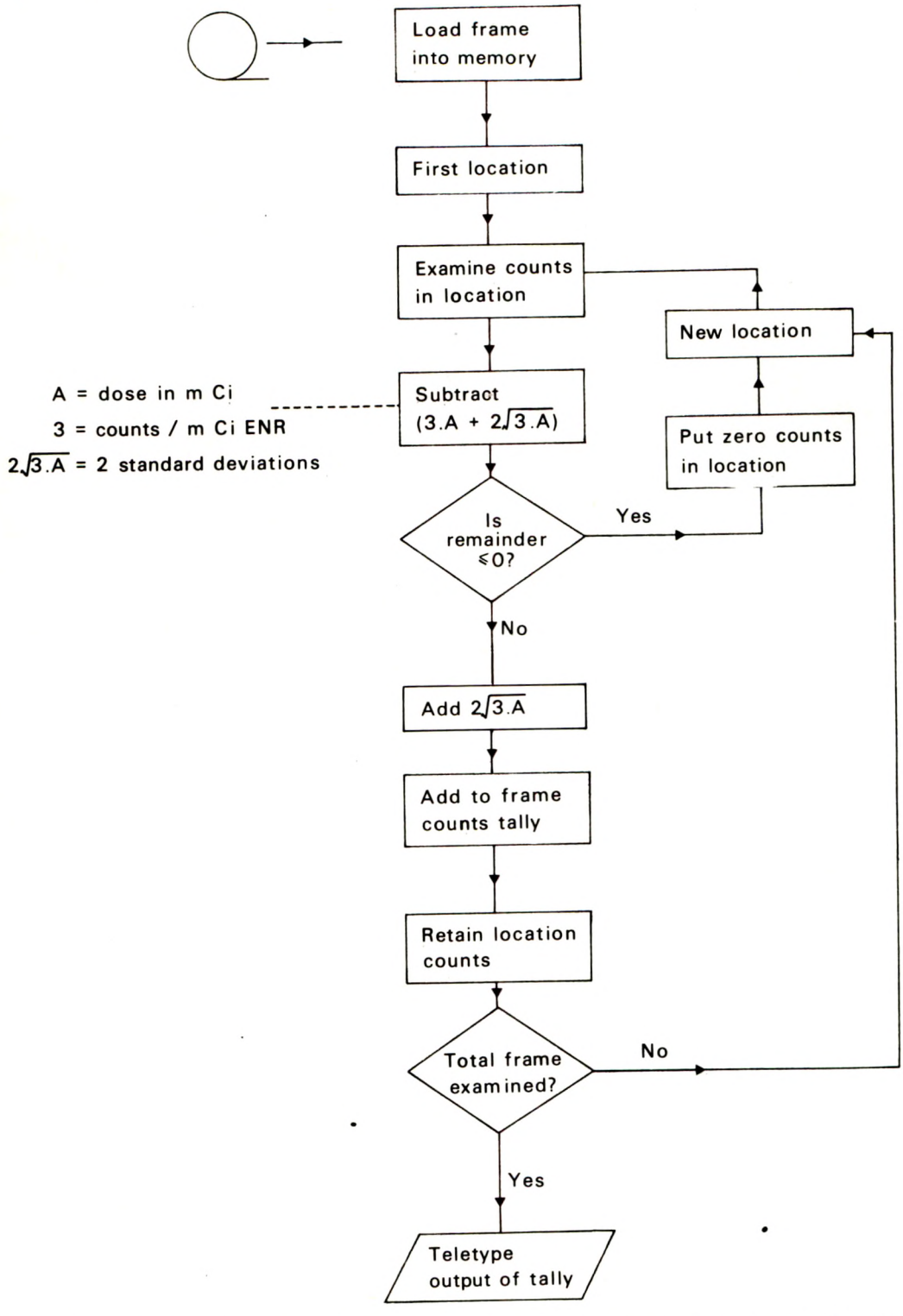

Fig. 5. Flow diagram showing the method for testing image matrix points for inclusion (or otherwise) in the net thyroid image, and subsequent tallying of processed counts.

APPENDIX I

The ENR-subtraction program incorporated a further refinement which may be worth noting.

Most procedures which have been described in the literature, dating from times of the single-probe uptakes, involve the simple subtraction of ENR counts (or rates) from gross counts, with appropriate adjustment for areas. Hurley *et al.*[8] described a procedure whereby the raw, computed ENR count had 2 standard deviations added to it and this total was subtracted from gross counts. This was done to ensure that virtually all background counts were eliminated, and would always give a smaller net thyroid count than the simple subtraction method.

In the system described in this paper, each matrix point is tested by subtraction ENR+2 standard deviations. If nonpositive counts remain, then that point is considered not to be part of the thyroid, and zero is left as the count at that location. If, however, the resultant count is positive, it is considered that that point represents thyroid tissue, not background, and only the raw background (ENR) is subtracted. The flow diagram for this subroutine is shown in Figure 5.

The computer memory then contains the processed counts, and the "net" image may be displayed for the scan record. However, the magnetic tape from which the frame was played still retains the gross counts.

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METASTATIC SEEDING ALONG THE SMALL BOWEL MESENTERY*

ROENTGEN FEATURES

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METASTATIC seeding in the abdomen follows a definite pattern of spread and localization. A previous report has shown that the commonest sites of lodgment and growth of seeded metastases clearly correlate with the pathways of flow of ascitic fluid.[5] Localization in the right lower quadrant at the lower end of the small bowel mesentery is identifiable in over 40 per cent of cases of intraperitoneal seeding. Their recognition permits the diagnosis of metastatic spread and often leads to uncovering the primary site, if unknown.

The purpose of this report is to document and illustrate the characteristic roentgen features in 8 cases of proved malignant seeding along the small bowel mesentery.

FIG. 1. The small bowel mesentery, illustrating its ruffled nature. A series of peritoneal recesses is formed along its right side. (Reproduced with permission of H. A. Kelly: Appendicitis and other Diseases of the Vermiform Appendix, and J. B. Lippincott Co., Philadelphia, 1909.)

ANATOMIC AND DYNAMIC CONSIDERATIONS

Both the anatomic dispositions of the mesenteries and the pathways of flow of any degree of ascitic fluid determine the deposition and growth of seeded metastases within the abdomen.[1,2,5]

The root of the small bowel mesentery extends from the left side of the second lumbar vertebra downward to the right, across the aorta and inferior vena cava, to the right sacroiliac joint, a distance of only about 15 cm. From the root, a series of mesenteric ruffles (Fig. 1) support the small bowel loops. It is these fan-like mesenteric extensions which contribute to the characteristic undulating nature and position of the coils of small bowel, which averages 15 to 20 feet in length. The distance between the intestinal and parietal mesenteric attachments is insignificant at the upper and lower extremities, and is greatest where the attachment crosses the spine. The depth of the mesentery, as a rule, does not exceed 20 to 25 cm. Distally, the mesentery most commonly inserts at the cecocolic junction and only occasionally in relation to the terminal ileum or the ascending colon.[7]

A series of peritoneal recesses is thus formed extending along the right side of the ruffled small bowel mesentery obliquely toward the right lower quadrant of the abdomen. It has been shown that these serve to pool collections of ascitic fluid.[2,5] The dynamic pathways of distribution and sequential spread of intraperitoneal fluid are dependent on mesenteric reflections and

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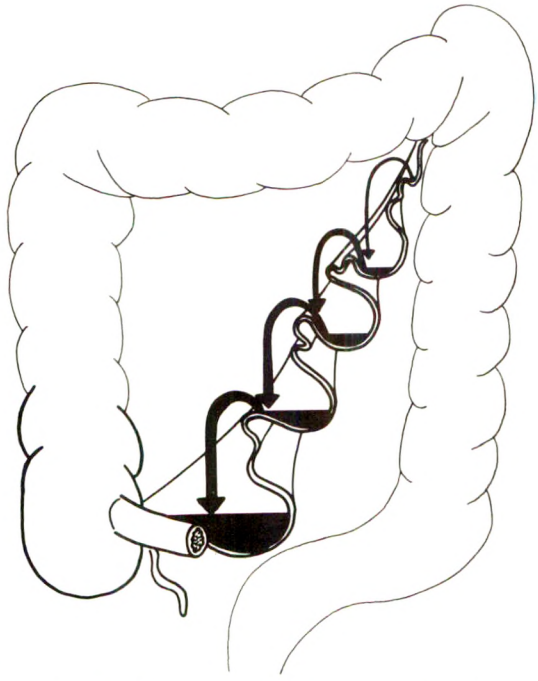

FIG. 2. The flow of ascites forms a series of pools within the recesses of the small bowel mesentery. The most consistent drainage is to its lower end, in relation to distal ileal loops and the cecum.

peritoneal recesses. The technique of peritoneography[3,5] has documented that spread occurs in a series of cascades or rivulets from one mesenteric ruffle to the next, directed along the axis of the small bowel mesentery toward the right lower quadrant in relation to distal ileal loops and the cecum (Fig. 2). It is here, within the lower recesses of the small bowel mesentery, that the most consistent pool of fluid forms before overflow into the pelvis occurs. Malignant cells are shedded into and transported by the induced ascitic fluid. The stasis, or pooling, favors the processes of deposition, fixation, and growth.

ROENTGENOGRAPHIC FINDINGS

Seeded deposits lodging within the lower recesses of the small bowel mesentery may be reflected by changes involving predominantly either ileal loops in the right lower quadrant or the cecum.

EFFECTS ON DISTAL ILEAL LOOPS

Symmetric growth within multiple adjacent mesenteric recesses results in discrete separation of ileal loops in the right lower quadrant. Angulated tethering of the mucosal folds indicates an associated desmoplastic response. The narrowed loops may be aligned in a parallel configuration which we describe as "palisading." The axis of the serosal masses as well as of the affected intestinal loops conform to the axis of the small bowel mesentery.

Figure 3 illustrates these changes in a 32 year old alcoholic bartender admitted with the provisional diagnosis of cirrhosis. Hepatomegaly and ascites were present. Barium studies showed gross narrowing and irregularity of the stomach, multiple points of obstruction involving the jejunum and striking palisading of distal ileal loops in the right lower quadrant characteristic of seeded metastases. Exploratory laparotomy documented a mucin-producing gastric adenocarcinoma with peritoneal carcinomatosis and hepatic metastases.

As the seeded growths become somewhat larger, they may displace the bowel loops in a gently arcuate manner (Fig. 4). The

FIG. 3. Case 1. Gastric carcinoma. Palisaded separation of ileal loops in right lower quadrant (arrows). Mucosal folds are mildly tethered. (Sites of obstruction are also present proximally.)

striking symmetry of size, mass displacement from the mesenteric border of the loops, and orientation to the mesenteric ruffles in the right lower quadrant characterize the process.

If the desmoplastic response to the seeded metastases is severe, marked fixation and angulation of ileal loops in the right lower quadrant result (Fig. 5). Serosal mass displacement may remain evident. The points of acute angulation tend to conform to the axis of the mesentery. Despite the narrowing and sharp course, obstruction may not be conspicuous.

If no significant fibrous reaction is elicited as the metastases increase in size, gross extrinsic mass displacement may be shown (Fig. 6; and 7, *A* and *B*). The mesenteric masses, however, tend to be multiple and they maintain their relationship to the lower small bowel mesentery. They displace ileal loops predominantly inferiorly and medially and may exert pressure upon the ascending colon medially and the proximal transverse colon inferiorly.

Fig. 5. Case III. Pancreatic carcinoma. Mass separation and angulation of fixed ileal loops in right lower quadrant from extensive desmoplastic reaction.

EFFECTS ON CECUM

Since the small bowel mesentery most commonly inserts at the cecocolic junction, seeded metastases within the most

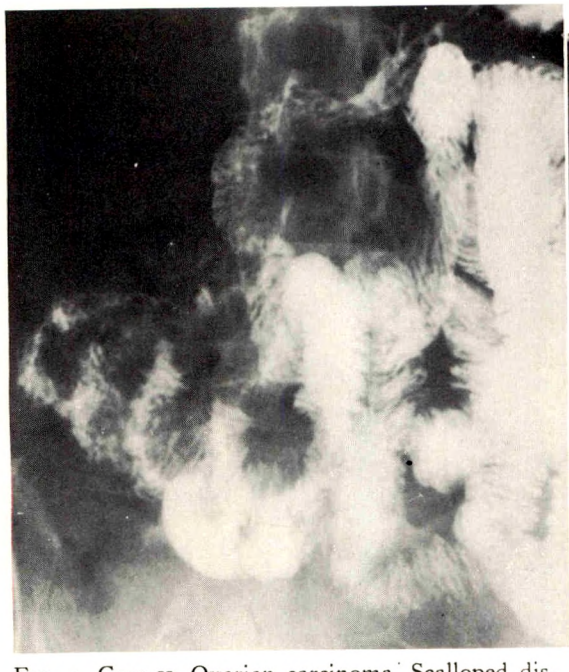

Fig. 4. Case II. Ovarian carcinoma. Scalloped displacement of ileal loops in right lower quadrant. Mucosal folds are mildly tethered. (Reproduced with permission of *Radiology*.[2])

Fig. 6. Case IV. Bronchogenic carcinoma. Seeded deposits result in gross mass displacement of ileal loops in right lower quadrant.

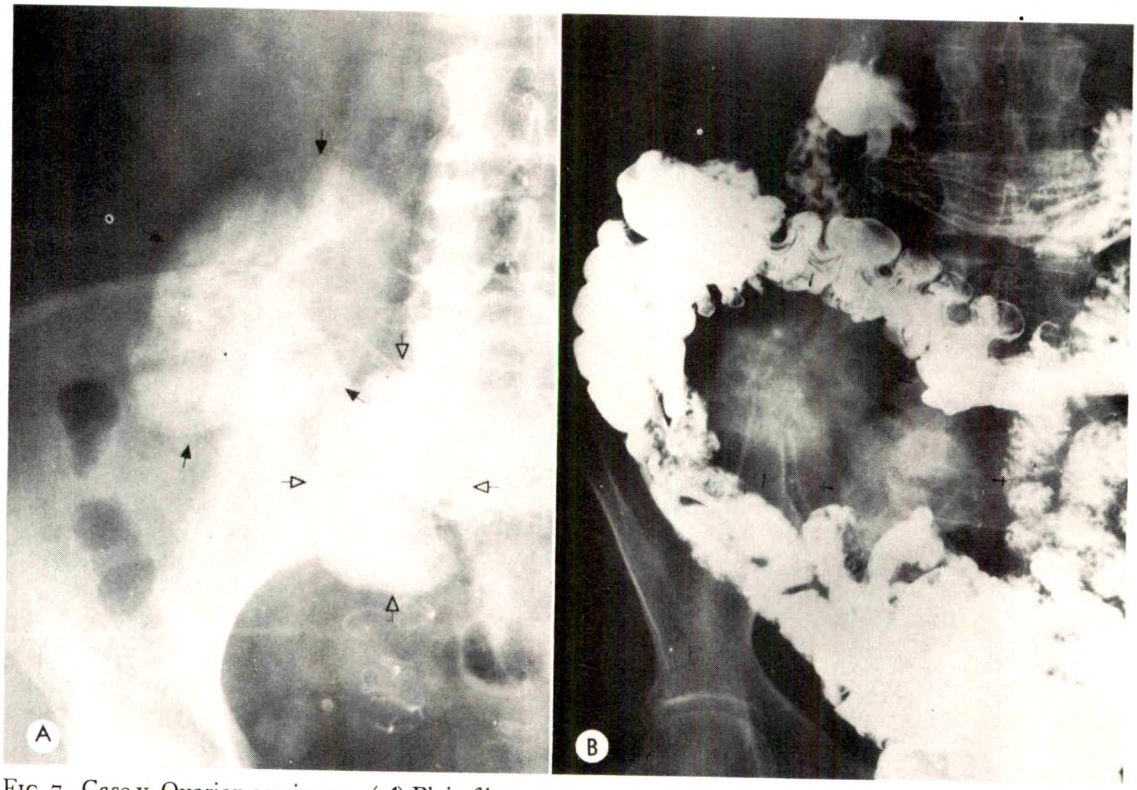

FIG. 7. Case v. Ovarian carcinoma. (*A*) Plain film roentgenogram. Two masses with psammomatous calcifications seeded in the right lower quadrant at the lower end of the small bowel mesentery are demonstrated. (*B*) Localization is further verified by displacement of the ileal loops and pressure upon the ascending and transverse colon. (*B* reproduced with permission from *Radiology*.[2])

distal recesses are shown typically by their pressure effects upon the cecum medially and inferiorly. The level of involvement is thus usually below the ileocecal valve in the caput of the cecum.

Figure 8 illustrates these changes in a 62 year old female with abdominal pain, a large right upper quadrant mass, and obstructive jaundice. The barium enema study documents tethered irregularity of the superior contour of the transverse colon indicating direct invasion[2,4] and a mass in the right lower quadrant eccentrically displacing the medial contour of the cecum, characteristic of seeded metastases. Autopsy disclosed a carcinoma of the gallbladder with invasion of the transverse colon and extensive peritoneal malignant seeding.

The extrinsic mass indenting the cecum may be smooth or lobulated (Fig. 9), of variable size (Fig. 10), and at times may

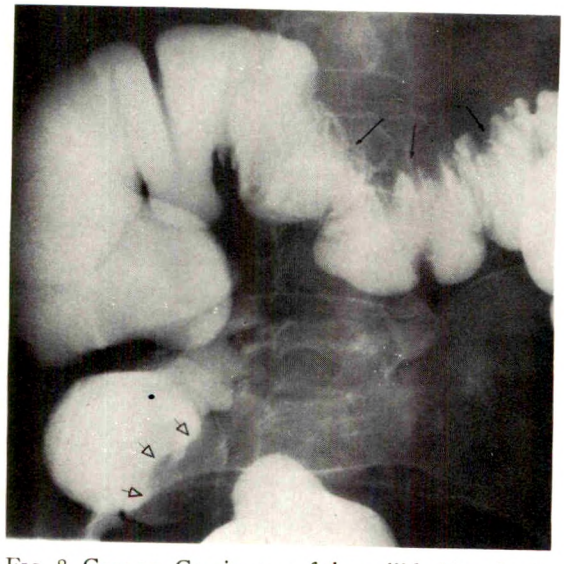

FIG. 8. Case VI. Carcinoma of the gallbladder. Seeding in the right lower quadrant results in a mass eccentrically indenting the medial contour of the cecum (open arrows). There is also direct invasion of the transverse colon (black arrows).

encircle the cecum (Fig. 11). If reflux is accomplished on the barium enema study, associated mass and desmoplastic changes involving the terminal ileum may also be appreciated (Fig. 9; and 10).

DISCUSSION

Sampson, in 1931, recognized that "the fluid arising from the peritoneal irritation caused by cancer cells escaping into the peritoneal cavity is the most important factor in the transportation of these cells. The latter go wherever the fluid goes. The amount of fluid, gravity, and the posture of the patient determine the site of the fluid and the presence of its cellular contents."[6] It was not until the clinical application of peritoneography, with the fluoroscopic and roentgen study of water-soluble contrast medium introduced into the peritoneal cavity, that the spread and localization of fluid were established.[1,5] The flow of ascites, determined by both gravity and the negative infradiaphragmatic pressure, is directed along the peritoneal recesses and

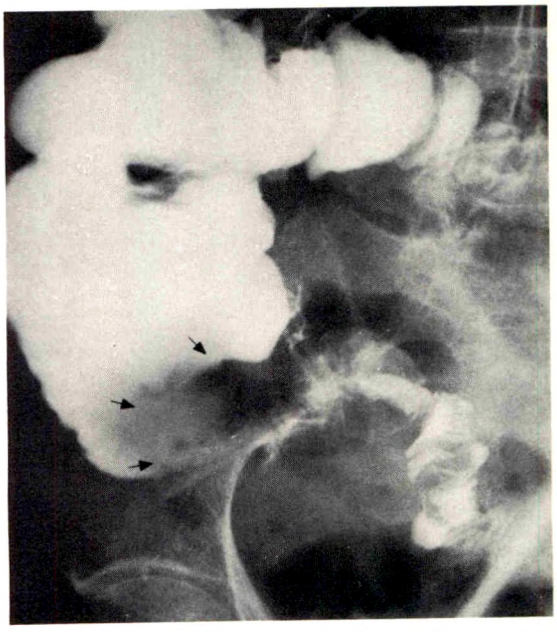

Fig. 10. Case VII. Pancreatic carcinoma. Large lobulated mass with nodular excrescences grossly indents the inferior contour of the cecum (arrows). There is also mass pressure upon the terminal ileum with fibrous angulation.

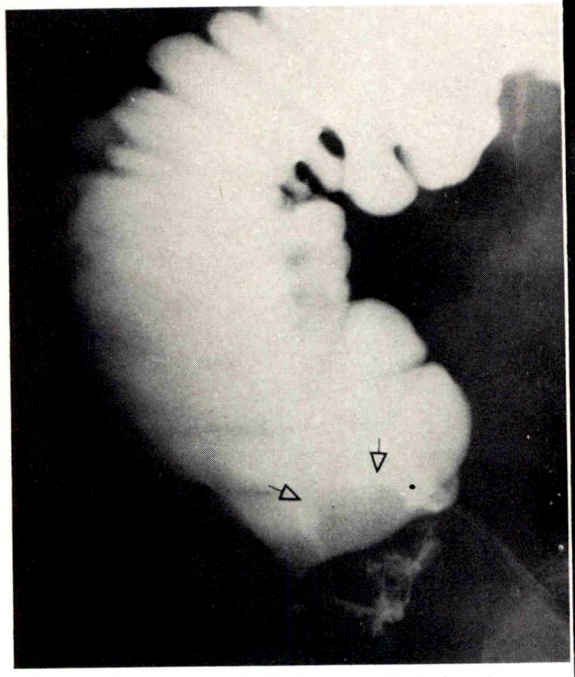

Fig. 9. Case I. Gastric carcinoma. Lobulated mass indents the inferior contour of the cecum (arrows). The distal ileum is angulated and deformed by mass impressions.

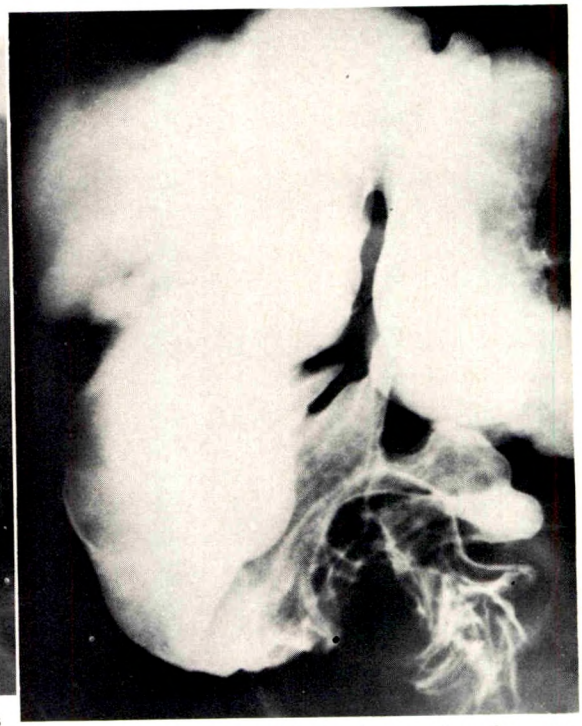

Fig. 11. Case VIII. Ovarian carcinoma. Annular mass narrowing of the apex of the cecum is demonstrated.

compartments in relation to the mesenteric attachments. In the right infracolic space, spread flows from one recess of the small bowel mesentery to the next lower and is continually directed along its axis to its lower extremity. The most consistent pool thus develops in relation to the distal ileal loops and cecum. The degree of ascites need not be great for the transportation and deposition of malignant cells. The seeded deposits coalesce and are then fixed to the serosal surfaces by a process of fibrinous adhesions which quickly become organized.[6] Localization at this site is identifiable in over 40 per cent of clinical cases.[2,5]

The roentgen changes involving the distal ileum range from discrete separation of adjacent loops, perhaps in a parallel "palisaded" configuration (Fig. 3), and multiple scalloped deflections (Fig. 4) to gross mass displacement (Fig. 6; and 7, *A* and *B*). The normal axis of individual mucosal folds perpendicular to the lumen of the bowel may be lost consequent to the desmoplastic response to the serosal metastases. This results in tethered angulation of mucosal folds which are therefore identifiable on the mesenteric borders. The most extreme fibrous reaction has been encountered in metastatic seeding from pancreatic carcinoma and mucin-producing gastric carcinoma. This may result in striking angulation and fixation of distal ileal loops (Fig. 5).

The mass changes upon the cecum involve typically its medial and inferior contours. They are not specific for seeded metastases and may simulate appendiceal abnormalities, other mesenteric masses, or even primary lesions of the cecum. However, they are almost invariably accompanied by the more characteristic changes involving distal small bowel loops. If first appreciated on a barium enema study, these can be identified by reflux into the terminal ileum (Fig. 9; and 10) or in a subsequent small bowel series.

The small bowel alterations are not difficult to distinguish from other common disease states. The lack of inflammatory features such as spasm, ulcerations, and sinus tracts and the characteristic spectrum of changes help in the differential diagnosis from regional enteritis, tuberculosis, amebiasis, and peritoneal adhesions. Palisading of ileal loops may be simulated rarely by retroperitoneal lymphadenopathy, as in lymphosarcoma, and carcinoid may be difficult to exclude in some cases of seeding with severe desmoplastic reaction. However, malignant seeding as a rule does not occur only in the right lower quadrant, but is accompanied by other characteristic roentgen changes in multiple specific sites. These include the pouch of Douglas at the rectosigmoid level, the left lower quadrant along the superior border of the sigmoid colon, and the right paracolic gutter lateral to the cecum and ascending colon.[2,5]

In the male, the primary carcinoma most commonly arises in the gastrointestinal tract (pancreas, stomach, colon) and in the female, the genital system (ovary). Only rarely is the primary carcinoma supradiaphragmatic in origin (Case IV).

SUMMARY

1. Intra-abdominal malignant seeding along the small bowel mesentery is roentgenologically identifiable.

2. The anatomic features of the small bowel mesentery and the pathways of flow of ascitic fluid along its peritoneal recesses determine the deposition and growth of seeded metastases.

3. Seeded deposits lodge particularly within the lower recesses of the small bowel mesentery and are reflected by typical changes involving distal ileal loops or the cecum.

4. These are characterized by (a) palisading, arcuate scalloped deflections or gross mass displacement of distal small bowel loops in the right lower quadrant, or (b) extrinsic indentations upon the medial and inferior contours of the cecum. Associ-

ated desmoplastic reaction may result in tethering of mucosal folds and angulated fixation of bowel loops.

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METASTATIC CARCINOMA SIMULATING INFLAMMATORY COLITIS*

By MORTON A. MEYERS, M.D., MICHAEL OLIPHANT, M.D., HIND TEIXIDOR, M.D., and PAUL WEISER, M.D.
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METASTATIC carcinoma to the colon is being encountered with increased frequency, both in advanced carcinomatosis of an already known primary lesion and as the initial manifestation of an occult neoplasm. Pathways of secondary involvement include hematogeneous dissemination, direct invasion and intraperitoneal seeding.[10] The commonest source of hematogenous spread to the colon is carcinoma of the breast. In a series of 337 autopsies in patients with breast carcinoma, Asch and associates[1] observed metastases to the colon in 15 (4.5 per cent). Of a group of 75 patients with advanced breast carcinoma who had laparotomy or autopsy, Graham[3] noted that 12 (16 per cent) demonstrated colonic metastases. In contrast, metastatic involvement of the large intestine by bronchogenic carcinoma is rare. Luomanen and Watson[6] report that of 676 patients who died of lung cancer only 2.2 per cent revealed metastases to the colon at autopsy. These are often small, serosal deposits. An abdominal primary lesion may spread to the large intestine by direct invasion along mesenteric reflections or from immediately contiguous sites; or by the process of intraperitoneal seeding. The malignancy arises most commonly in the stomach, pancreas, or ovary.[10,11]

Metastatic carcinoma to the large intestine may be easily mistaken for primary inflammatory processes, such as granulomatous or ulcerative colitis, both clinically and roentgenologically. Isolated case reports in the literature attest to the difficulty in diagnosis and, in particular, the mimicry of inflammatory colitis.[2,4,8,17] Diarrhea may be a conspicuous clinical presentation, occasionally of several years' duration.[4,8,17] At times, it may be associated with some blood and mucus.[17] Roentgenographic changes also often show striking similarities to inflammatory colitis. Melnick and Rosenholtz[8] have observed a case of metastatic breast carcinoma resembling ulcerative colitis which demonstrated loss of the normal mucosal pattern and haustral markings, narrowing and foreshortening of the colon, multiple pseudo-ulcerations, and skip areas of strictures. Stoodley and Mann[17] have recently described 3 patients with metastatic carcinoma to the colon simulating Crohn's disease clinically and roentgenographically. Findings on barium enema studies included asymmetric and multiple "purse-string" strictures, cobblestone and fissure formations, and rose-thorn spiculations. In 1 of their cases, the gastric primary lesion was not apparent at the time of the colonic changes but was evident 4 years later.

The individual roentgen features of secondary involvement of the colon have been detailed by several authors,[5,18] but the principal emphasis has been on discrimination from a primary mucosal neoplasm. We have encountered 12 cases of metastatic carcinoma which were initially considered as ulcerative or granulomatous colitis clinically and roentgenologically. Diarrhea, occasionally with bloody mucus, tenesmus and flatulence often dominated the clinical presentation. Characteristic roentgen findings include mucosal thickening, nodular masses, multiple and eccentric strictures, asymmetric involvement, pseudosacculations, spiculations of contour, and frequent associated terminal ileal involvement. It is apparent that the changes share many common features with inflammatory colitis,

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particularly Crohn's disease. Failure to recognize their true malignant nature may delay or prevent the pursuit of appropriate diagnostic studies. We have noted that associated discrete changes and the distribution of colonic involvement readily distinguish metastatic disease from inflammatory colitis. These specific features are dependent upon pathways of spread, growth characteristics, and local tissue response. In other cases, recognition of the overlap in gross findings leads to further studies.

MATERIAL AND ROENTGENOGRAPHIC OBSERVATIONS

HEMATOGENOUS DISSEMINATION

The difficulty encountered at times in distinguishing continuous irregular mural thickening with narrowing of the lumen due to granulomatous colitis or metastatic intramural infiltration is strikingly illustrated by Case 1. This 56 year old female had had a right and a left radical mastectomy 7 and 3 years prior to admission. She had been well during the interval but presented with a 4 month history of diarrhea, occasionally blood-tinged. Barium enema examination disclosed findings consistent with right-sided granulomatous colitis (Fig. 1). The ascending colon was diffusely and somewhat irregularly narrowed, the mucosal and haustral patterns were effaced, and occasional nodular filling defects and serrations resembling minute ulcers were present. A patulous ileocecal valve was evident with probable involvement of the most distal portion of the ileum. While on conservative medical therapy for presumptive granulomatous colitis, she developed a palpable right lower quadrant mass which led to an exploratory laparotomy. This documented the presence of peritoneal carcinomatosis and dense intramural infiltration of the ascending colon from metastatic breast carcinoma.

Asymmetric involvement of the right colon and narrowing of the terminal ileum, two of the pathologic and roentgenographic hallmarks of granulomatous ileocolitis, are

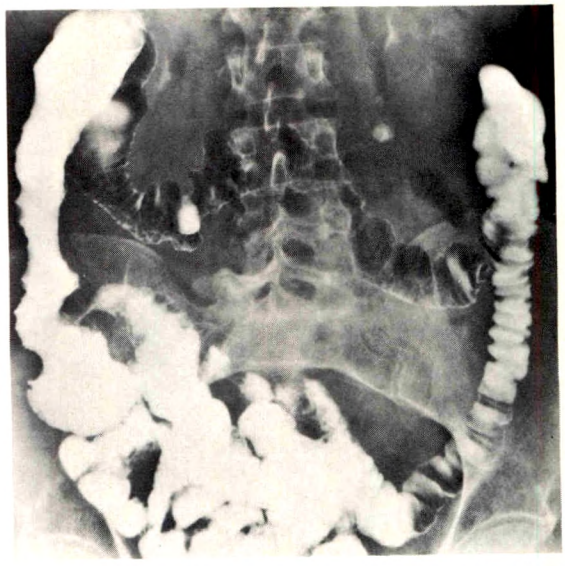

Fig. 1. Case 1. *Metastatic breast carcinoma to right colon.* The entire ascending colon is encased by densely cellular submucosal secondary deposits. The lesion strikingly resembles granulomatous colitis.

illustrated by Case 11 (Fig. 2*A*). This 58 year old female had a radical mastectomy for breast carcinoma 8 years previously and presented with diarrhea. The associated finding of multiple skip sites of narrowing and alternating dilatation within the small bowel loops (Fig. 2*B*) was taken as further evidence of inflammatory disease, and the patient was treated over a period of 2 years at another hospital for granulomatous enterocolitis. With the development of constipation and a rectosigmoid stricture, a deep biopsy showed metastatic breast carcinoma.

We have also encountered 2 cases of hematogenous breast metastases localized to the rectum, occurring as late as 19 years following radical mastectomy. Barium enema examination findings closely simulated those of a primary inflammatory proctitis (Fig. 3, *A* and *B*; and 4). While a superficial biopsy may show only subepithelial inflammatory cells, deep biopsy confirms the malignant nature of the rectal stricture.

Skip areas of involvement within the colon itself may be produced by hematogenous metastases (Fig. 5). These may

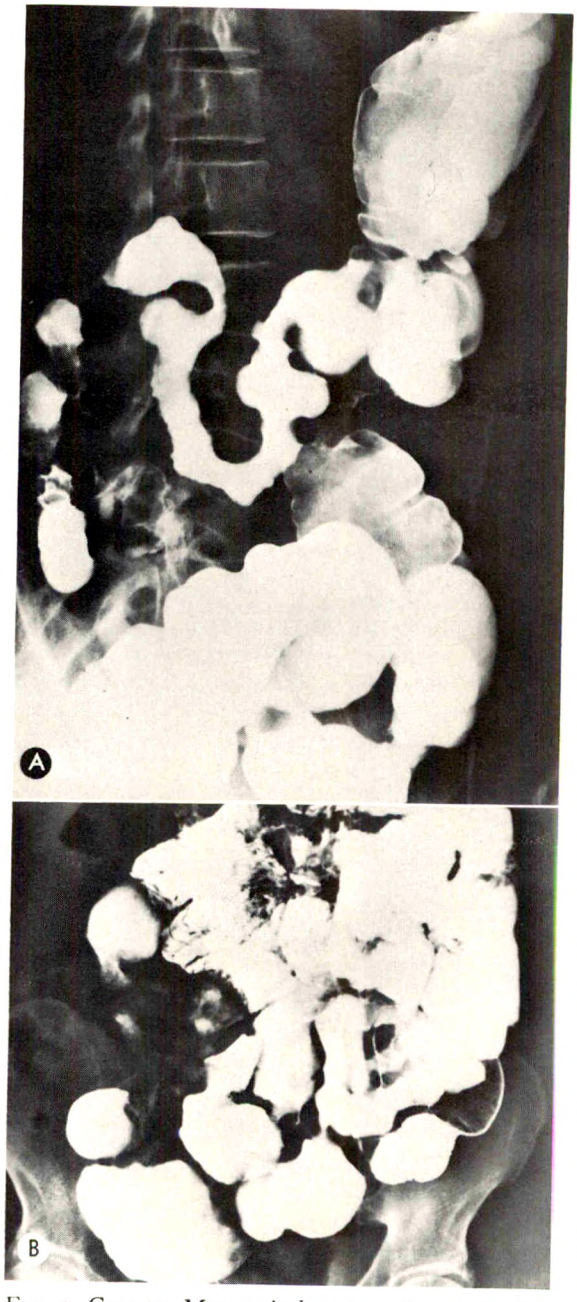

FIG. 2. Case 11. *Metastatic breast carcinoma to right colon and small intestine simulating granulomatous enterocolitis.* (*A*) The ascending and proximal transverse colon show asymmetric narrowing, scattered pseudosaccular formation, loss of the normal haustral and mucosal pattern, and the appearance of marginal ulcerations. The terminal ileum is also involved. (*B*) Within the small bowel, there are multiple skip areas of strictures with intervening dilatation. Hematogenous submucosal cellular deposits account for the colonic and small bowel changes.

demonstrate many of the characteristics of Crohn's disease, including asymmetry, gently sloping borders, varying lengths, pseudosacculations, and the appearance of fairly deep transverse ulcerations. At other times, these features of eccentric mural involvement may be conspicuous in a localized segment (Fig. 6, *A* and *B*).

DIRECT EXTENSION

Similar colonic abnormalities may be produced by direct extension from an adjacent primary malignancy. This is seen most commonly from spread of a scirrhous gastric carcinoma, itself often clinically occult, along the gastrocolic ligament.[10,15] Diarrhea may dominate the clinical picture and the barium enema examination findings may be misinterpreted as most consistent with inflammatory colitis, particularly Crohn's disease, without the pursuit of a diagnostic upper gastrointestinal series. In the 46 year old female, illustrated in Figure 7*A*, presenting with diarrhea and weight loss, unilateral mural induration and fixation is present along the entire length of the superior border of the transverse colon. The uninvolved inferior contour retains its pliability so that its haustral recesses are thrown into pseudosacculations. The detail in Figure 7*B* shows extension of the process to the right colon with nodular filling defects and thickened mucosal folds. Within the proximal transverse colon, cobblestone-fissuring consisting of both linear and transverse ulcers is indicated. This complex of features initially suggested granulomatous colitis. However, further inspection revealed that the mucosal folds along the superior haustral row of the transverse colon were definitely tethered; rather than maintaining a normal relationship perpendicular to the lumen, they were conspicuously angulated at random axes. Recognition of this distinctive finding as indicative of a desmoplastic response in the adjacent peritoneal reflection and serosa[10,11,15] led to an upper gastrointestinal series. This confirmed the presence of a scirrhous carcinoma of the stomach.

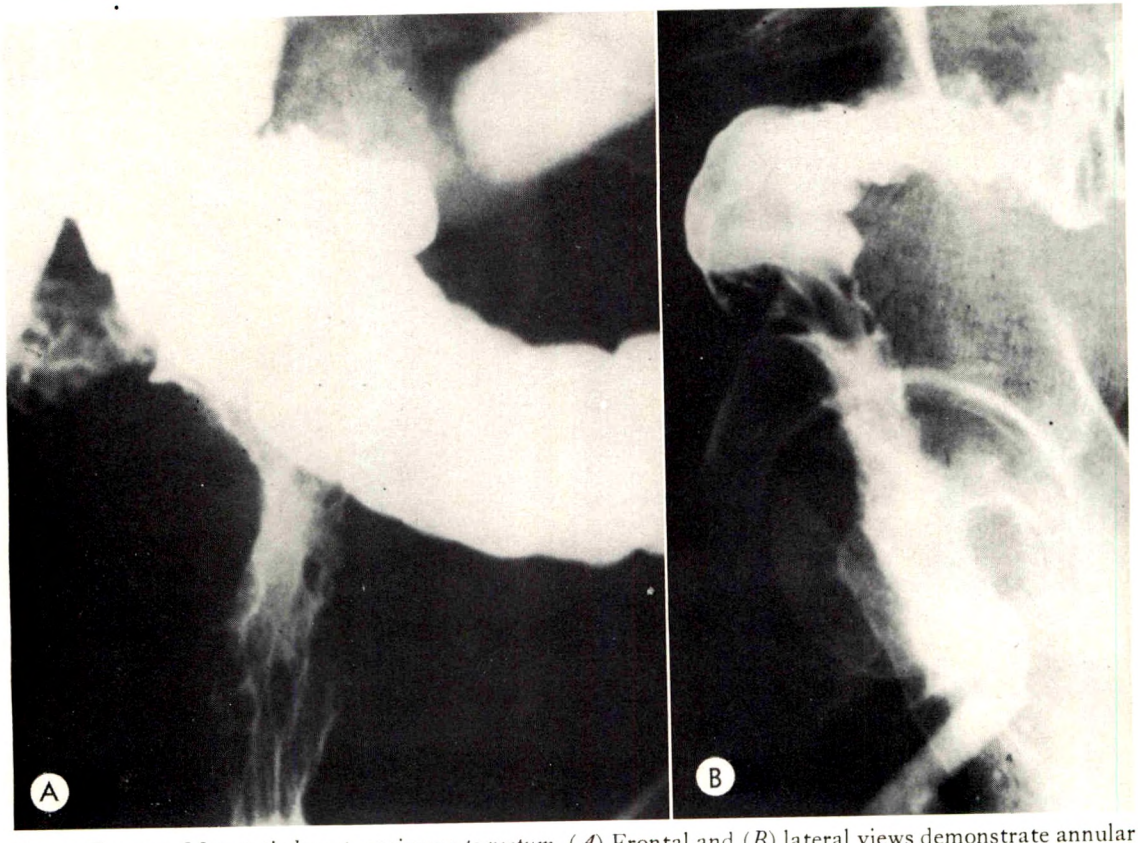

Fig. 3. Case III. *Metastatic breast carcinoma to rectum.* (*A*) Frontal and (*B*) lateral views demonstrate annular narrowing of the rectum with nodularity and distortion of the mucosal folds and the appearance of multiple cobblestone ulcerations.

Further extension may so involve the ascending colon that it becomes indistinguishable from granulomatous colitis. The desmoplastic response accompanying the metastatic spread in Case VIII (Fig. 8) resulted in foreshortening, narrowing of the lumen, nodular irregularities, loss of the haustral pattern with gross mucosal distortion, and spiculations of contour.

Fig. 4. Case IV. *Metastatic breast carcinoma to rectum.* Irregular mucosa with the appearance of cobblestone ulcerations within a markedly narrowed rectum. Note gradual transition to normal, distended sigmoid segment.

FIG. 5. Case V. *Metastatic breast carcinoma to colon.* Skip areas of narrowing with localized loss of the haustral and mucosal pattern involve the ascending, transverse, sigmoid, and rectosigmoid colon. Pseudosacculations reflect the asymmetric nature of the process. Fairly deep transverse ulcers appear to project from the narrowed segment in the transverse colon.

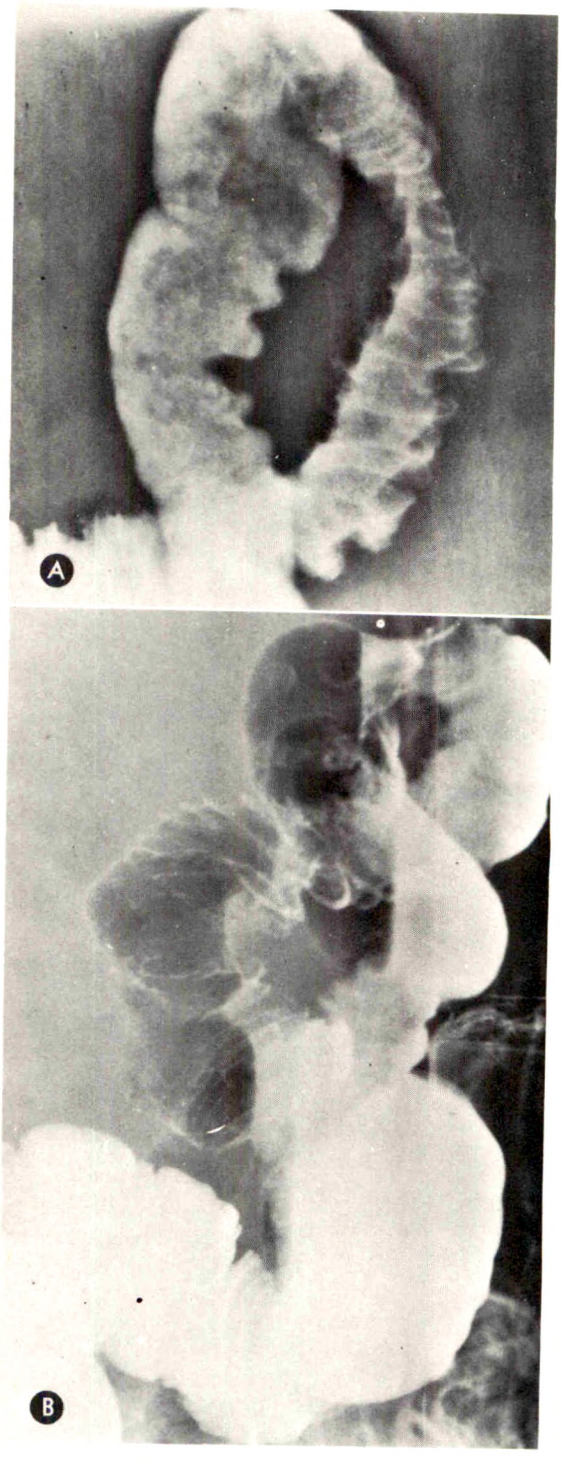

FIG. 6. Case VI. *Metastatic breast carcinoma to colon.* (*A* and *B*) Within the splenic flexure, asymmetric mural involvement is shown by the indurated nodular contour, thickened and distorted mucosal folds, and the appearance of ulcerations.

INTRAPERITONEAL SEEDING

Intraperitoneal seeding may occur as the only mode of intraabdominal spread or in conjunction with direct extension. Case IX illustrates the segmental effects upon the colon from both processes, mimicking many of the features of Crohn's disease. A barium enema study in a 36 year old male revealed irregular haustral distortion and fixation of the transverse colon (Fig. 9*A*). The cecum and proximal ascending colon were narrowed and non-distensible, and a prominent mass deformity involved the sigmoid colon, particularly its superior aspect (Fig. 9*B*). A scirrhous carcinoma of the stomach was then demonstrated. This was confirmed at surgery, with severe desmoplastic reaction accompanying the direct extension down the gastrocolic ligament and multiple sites of intraperitoneal seeding.

Other instances of malignant seeding

may also closely simulate Crohn's disease roentgenographically (Fig. 10, *A* and *B*; 11; and 12).

DISCUSSION

There are striking similarities of metastatic involvement to intrinsic inflammatory disease of the colon, particularly Crohn's disease (Table 1). Clinically, diarrhea may persist for some duration and others have also noted[1] that this may occur several years after treatment of a primary malignancy or in the presence of an occult

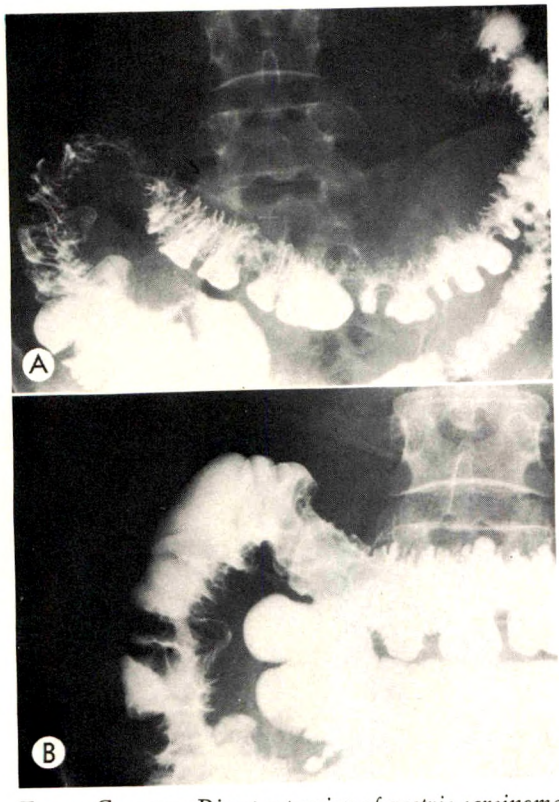

FIG. 7. Case VII. *Direct extension of gastric carcinoma to colon.* (*A* and *B*) Barium enema examination features resembling Crohn's disease include unilateral involvement of the transverse colon, pseudosacculations, the appearance of cobblestone fissuring, and thickened mucosa. There is involvement of the right colon as well. Note the angulated tethering of the mucosal folds along the superior border of the transverse colon. Spread has occurred down the gastrocolic ligament from a linitis plastica carcinoma of the stomach. (Courtesy of Bert Lincoln Pear, M.D., Porter Memorial Hospital, Denver, Colorado.)

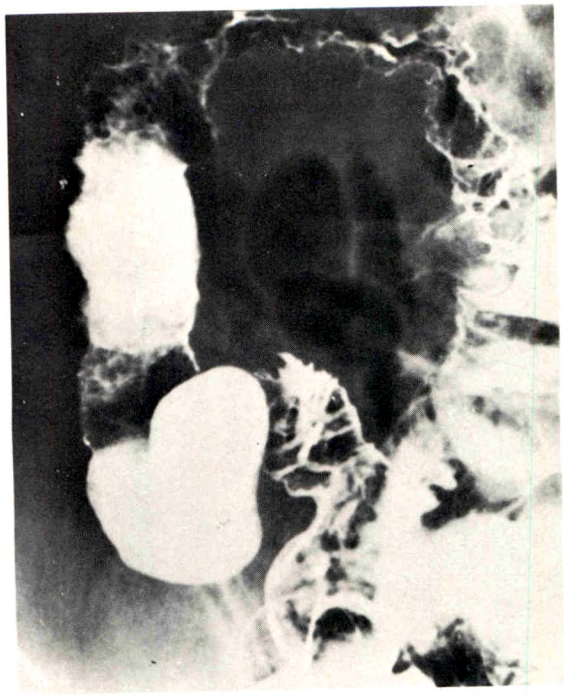

FIG. 8. Case VIII. *Direct extension of gastric carcinoma to colon.* Spread from a scirrhous carcinoma of the stomach in this 52 year old female results in changes in the right colon indistinguishable from Crohn's disease. (Courtesy of Barry Held, M.D., Booth Memorial Hospital, Flushing, New York.)

neoplasm. In granulomatous colitis, the chronic inflammation of the entire wall, particularly the submucosa, results in thickening and rigidity of the wall, narrowing of the lumen and a coarsely nodular surface, with asymmetric and skip areas of involvement.[7] There is often right-sided colonic involvement. That these features can be duplicated by metastatic disease is illustrated by the cases in this report. Breast metastases are usually deposited in the mucosa and submucosa,[3] but occasionally infiltrate the entire thickness of the colonic wall.[8] These may result in essentially similar gross changes as in Crohn's disease on a barium enema examination.

The pathogenesis of the overlap in gross and roentgen findings is largely dependent upon pathways of spread, growth characteristics and local tissue response. No significant fibrous reaction accompanies hematogenous breast metastases. Both

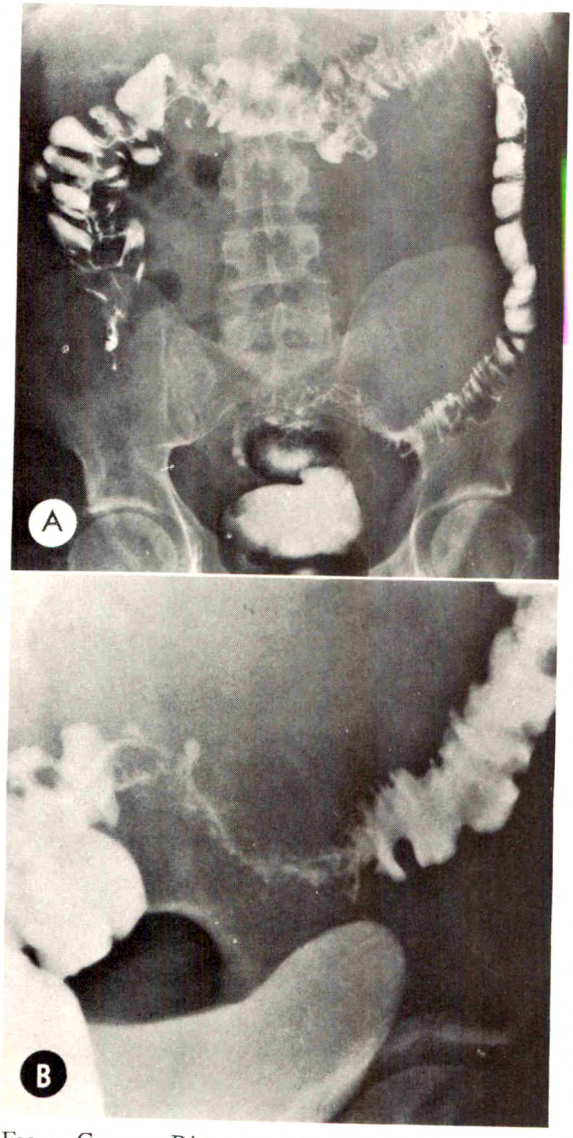

FIG. 9. Case IX. *Direct extension to the transverse colon and seeded metastases to the cecum and sigmoid colon from scirrhous gastric carcinoma.* (*A*) Barium enema examination shows "skip" involvement. (*B*) Detail view of the sigmoid colon demonstrates narrowing with predominant mural involvement on superior contour.

direct extension to the colon from an adjacent primary lesion and seeded metastases are often associated with a highly desmoplastic response and produce typically asymmetric changes. Fixation of one wall by the malignant process results in pseudosacculations from the opposing normal wall. The appearance of ulcers (Fig. 1; 2*A*; and 3–6), occasionally assuming a cobblestone nature (Fig. 5; 6; and 7*B*), held to be virtually pathognomonic of granulomatous colitis, results from fixed buckling of the mucosa.

However, discrete roentgenologic changes and the sites of lesions may be evident which distinguish metastatic involvement from inflammatory conditions (Table II). Direct extension from a primary gastric carcinoma characteristically involves first the superior haustral row of the transverse colon.[10,15] This spread follows the mesenteric plane of the gastrocolic ligament. The associated desmoplastic response is revealed by the diagnostic tethering of the mucosal folds at this site and the projection of pseudosacculations from the inferior haustral row. Similar changes may be a sign of peritoneal seeding, but its distribution has been shown to involve preferential sites related to the dynamic circulation of ascitic fluid.[9–11,14] These include the anterior surface of the rectosigmoid, the superior contour of the sigmoid colon, and the right lower quadrant and right paracolic gutter in relation to the terminal ileum and cecum. Growth of seeded deposits within the pouch of Douglas may result in a stricture of the rectosigmoid (Fig. 11). Seeded metastases in the region of the sigmoid mesocolon may be revealed by their effect preponderantly upon the superior border of the sigmoid (Fig. 9, *A* and *B*; and 12). Deposition and growth within the lower recesses of the small bowel mesentery may progress to involvement of both the terminal ileum and right colon (Fig. 9, *A* and *B*; and 10, *A* and *B*).

In those cases where differentiation is difficult, histologic documentation or other roentgenographic studies may be necessary. Standard biopsies of a stricture through the colonoscope may show only nonspecific, chronic inflammatory changes even in the presence of metastases.[17] Deep biopsies, however, may reveal the true nature of the stricture. Stoodley and Mann[17] also recommend cytologic analysis of any ascitic fluid, and demonstrated the

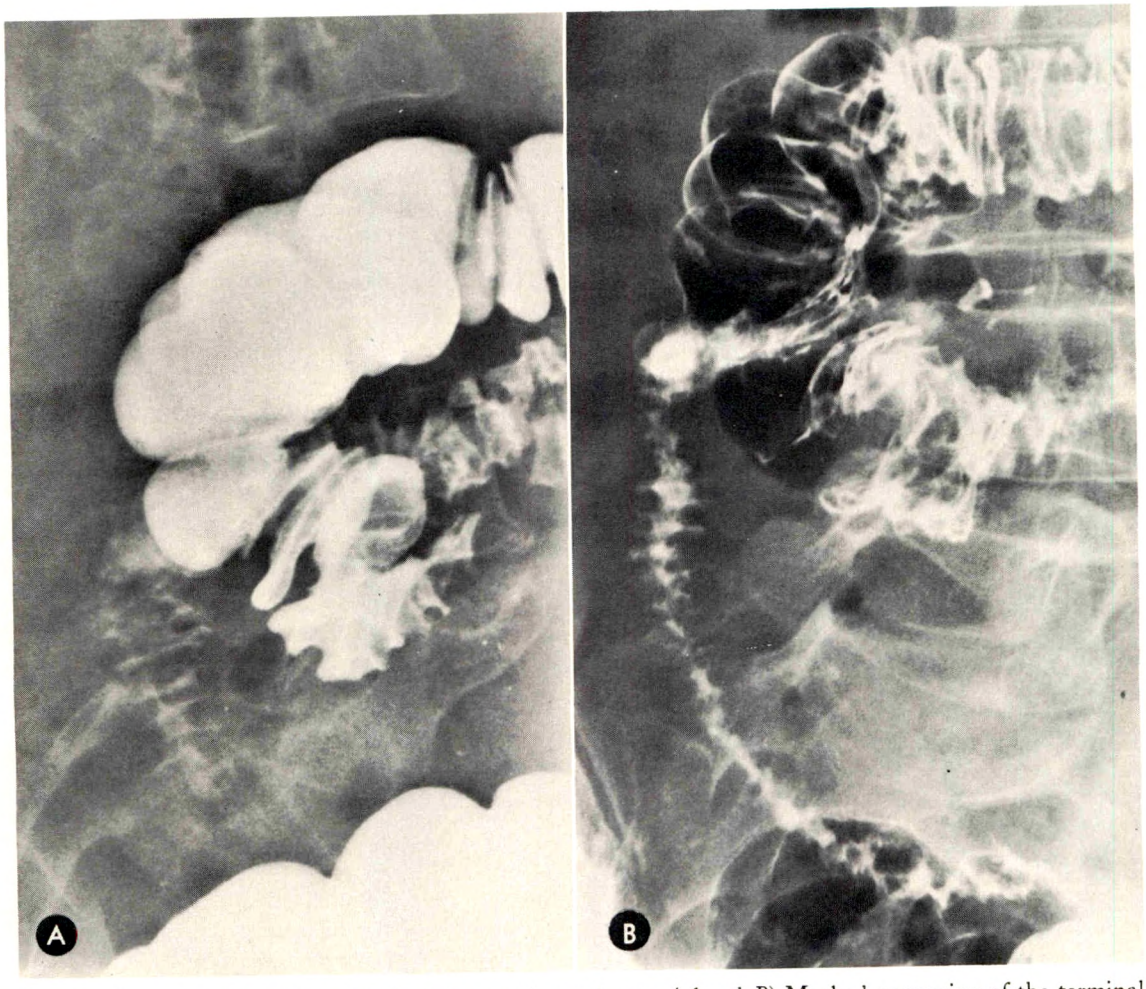

Fig. 10. Case x. *Malignant seeding from pancreatic carcinoma.* (*A* and *B*) Marked narrowing of the terminal ileum and mural distortions of the cecum closely mimic granulomatous ileocolitis. (Courtesy of Kevin Macken, M.D., Francis Delafield Hospital, New York, New York.)

value of selective angiography in 1 of their cases where interruptions in the marginal artery supply to the colon indicated carcinomatosis rather than Crohn's disease. Peritoneography[12,13] is also capable of demonstrating increased mural thickness of the bowel and any adjacent serosal or mesenteric masses.

CONCLUSION AND SUMMARY

Metastatic carcinoma to the colon may be mistaken for inflammatory colitis, particularly Crohn's disease, both clinically and roentgenologically. Characteristic changes include mucosal thickening, nodular masses, multiple and eccentric strictures, asymmetric involvement, pseudosacculations, and spiculations of contour.

This report, based upon experience with 12 cases, establishes the distinctive roentgen features of metastatic disease to the colon from a variety of primary sites. It is shown that these changes are dependent upon pathways of spread, growth characteristics, and local tissue response.

The clinical importance of making this differential diagnosis is two-fold. A patient with an occult or a known primary malignancy may present clinically with metastatic disease to the colon masquerading

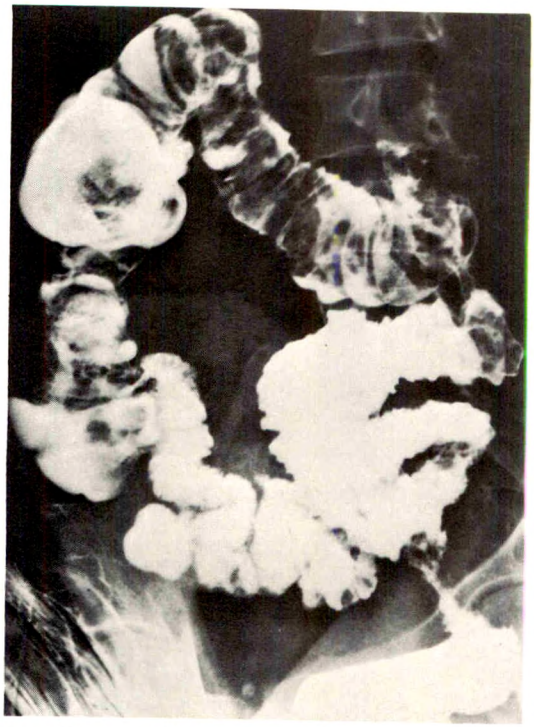

FIG. 11. Case XI. *Malignant seeding from gastric carcinoma* resulting in irregular deformity of the ascending colon and a rectosigmoid stricture. Skip sites of involvement resemble granulomatous colitis. The underlying, localized anaplastic carcinoma of the stomach in this 46 year old male was not clinically identified until operation, which also revealed widespread peritoneal implants. (Courtesy of Kevin Macken, M.D., Francis Delafield Hospital, New York, New York.)

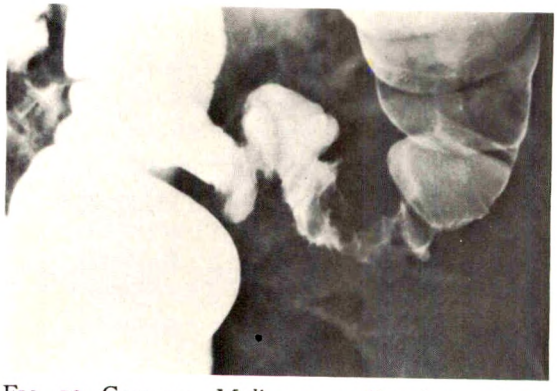

FIG. 12. Case XII. *Malignant seeding from mucin-forming gastric carcinoma.* Seeded deposits with desmoplastic reaction simulate localized granulomatous colitis of the sigmoid.

TABLE I

ROENTGEN FEATURES

Feature	Inflammatory Colitis	Metastatic Carcinoma Simulating Inflammatory Colitis
Mucosal thickening	+	+
Nodular masses	+	+
Skip areas	+	+
Multiple eccentric strictures	+	+
Asymmetric involvement	+	+
Pseudosacculations	+	+
Spiculations of contour	+	+
Cobblestone appearance	+	+
Abnormal terminal ileum	+	+
Tethering of mucosal folds	−	+
Fistulas	+	−

as inflammatory colitis. Recognition of the characteristic roentgenologic changes immediately either leads to a search for the primary neoplasm or establishes the diagnosis of widespread disease.

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Table II

DIFFERENTIAL ROENTGEN FEATURES OF METASTATIC DISEASE SIMULATING INFLAMMATORY COLITIS

Pathway of Spread	Most Common Primary Source	Growth Characteristics	Localization
Hematogenous dissemination	Breast	Mucosal, submucosal, or full wall thickness; not desmoplastic	Nonspecific for site or border
Direct invasion			Inferior border of sigmoid
(I) Contiguous structures	Ovary		
(II) Via mesenteric reflections	Stomach	Desmoplastic	Transverse colon, superior border
	Pancreas		Transverse colon, inferior border
Intraperitoneal seeding	Stomach		Sites related to ascitic flow:
	Pancreas	Desmoplastic	(1) anterior rectosigmoid
	Ovary		(2) RLQ: terminal ileum and cecum
	Colon		(3) superior border of sigmoid
			(4) lateral cecum and ascending colon

RLQ=right lower quadrant.

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CARCINOMA OF THE CERVIX: A TIME DOSE ANALYSIS OF CONTROL AND COMPLICATIONS*

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THE combination of intracavitary and external beam radiotherapy in the management of carcinoma of the cervix makes both dose prescription and comparison of differing treatment techniques difficult. Two empirically derived methods of calculation are currently widely used. The Manchester system combines external and intracavitary doses at 2 points, A and B, which represent the paracervical triangle and the lateral pelvic (obturator) lymph nodes, respectively.[10] Recommended tumor doses and normal tissue tolerance are expressed in the same terms.

From the Paris school there has evolved a system of dose prescription and tolerance prediction based on external beam dosage in rads plus intracavitary radiation expressed in milligram hours (mgh). For each stage of disease, recommended combinations of internal and external treatment have been published.[5]

In the hands of their proponents both systems prove suitable to guide treatment of disease with low complication rates. However, neither system adequately expresses the influence of variables such as different intracavitary dose rate, variation of isodose distribution due to anatomic differences, the inhomogeneity of dose throughout the tumor volume and the dose to normal structures such as bladder and rectum.

The advent of afterloading applicators and computerized isodose distributions for intracavitary treatment makes both systems partially obsolete. Treatment can now be more accurately tailored to the individual patient's tumor and anatomy. Yet a dose prescribing formula is necessary and some method of predicting tumor control, probability of complication, and a way to compare differing treatment regimens is needed.

In 1974, Ellis and Sorensen[3] published a method for calculating and expressing the combined dose of internal and external radiation treatment of cancer of the cervix in terms of Nominal Standard Dose (NSD). Buchler *et al.*[1] studied the correlation of NSD with complications in a large number of patients treated for cancer of the cervix.

The present study discusses the use of NSD as a predictor of both tumor control and complications. A comparison is made with other methods currently in wide use.

MATERIAL AND METHOD

From 1963 to 1972, 532 patients with cervical cancer were seen at the Walter Reed Army Medical Center. The patients were clinically staged jointly by radiotherapy and gynecology staffs. In cases of disagreement patients were assigned to the lower stage. Patients undergoing hysterectomy with cancer diagnosed postoperatively were unstaged (Stage U). Pathologic diagnosis was obtained on all patients and reviewed at the Armed Forces Institute of Pathology. The International Federation of Gynecology and Obstetrics (FIGO)

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staging system was used for all patients[2] (Table 1).

During the 10 year period under study, 147 1A and 1B patients who were medically fit underwent radical surgical treatment and most of these patients were reported by Park *et al.*[12] elsewhere. Two patients have been excluded; 1 was treated with chemotherapy only and 1 died of hepatitis untreated. The remaining 383 patients were treated with radiotherapy and are the subject of this analysis.

Supervoltage external treatment was administered with a 2 MVP resonant transformer, cobalt 60 teletherapy unit, or 4 MV linear accelerator. Intracavitary treatment was given by Manchester, Ernst or Fletcher-Suit applicator. When possible 1 or 2 internal applications were made. External treatment generally consisted of anteroposterior whole pelvic fields, often with some mid-line shielding. Occasionally rotational pelvic treatment with cobalt 60 was given.

Intracavitary doses, expressed in rads/hour at Points A and B were, until 1970, calculated individually or obtained from standard Ernst tables. Since that time they have been obtained *via* computer (the M. D. Anderson Radcomp Program).

In the calculation, doses at Points A and B were averaged in cases where significant differences existed. External beam doses were calculated in rads to the patient's midplane mid-line. No allowance was made for penumbra, transmission through or scatter by shields.

TABLE I

FIGO STAGING*

Stage	
IA	Not detectable by clinical examination
IB	Other cases limited to cervix
IIA	Involvement of upper 2/3 of vagina
IIB	Involvement of parametrium
IIIA	Extension of lower 1/3 of vagina
IIIB	Extension to pelvic wall
IV	Tumor in bladder, rectum or out of pelvis

* *Acta obst. et gynec. scandinav.*, 1971, *50*, 1–7.

NSD calculations represent ret doses at the completion of therapy. For the external beam contribution to Points A and B, the standard formulation is used.[4] For the intracavitary applications, the dose in rets is equal to the dose delivered to the particular point divided by a dose rate correction factor, F, which gives "equivalent rads." Equivalent rads is defined as the number of rads which, if delivered at 35.7 rads/hr. (or 6,000 rads in 7 days), would produce the same effect on normal skin or mucous membrane as the dose given.

$$\text{Intracavitary rets to Point A} = \frac{\text{Dose (rads)}}{F} \text{ to Point A} \times \frac{1{,}800 \text{ (rets)}.}{6{,}000 \text{ (rads)}}$$

The values for F range from 1.12 for 15.0 rads/hour to 0.682 for 100 rad/hours. The formulation yields a value of 1,728 rets for an application of 4,000 rads given in 72 hours. As significant delays in the treatment were rare, no decay of the accumulated ret dose was necessary. (Orten and Ellis[11] recommend decay for split course therapy.)

RESULTS

When the patient population was analyzed, the effect of a relatively uniform treatment policy applied over the decade reviewed was noted. Of 200 clinical Stage 1 patients, 164 were selected for surgery. The 36 treated definitively with irradiation were thought to be poor surgical candidates because of medical illnesses including hypertension, diabetes, obesity, previous stroke, or other cardiovascular disease. Of the 164 patients explored, 147 underwent a radical Wertheim-Taussig hysterectomy and bilateral lymphadenectomy with the finding of adequate surgical margins and no metastatic disease in the lymph nodes. The remaining 17 patients underwent postoperative irradiation because of metastatic disease in pelvic lymph nodes (12), or tumor at the resection margin (2). Two patients were explored but not resected because of positive aortic lymph nodes, and

TABLE II

TREATMENT MODALITY

	Stage	XRT* Only	Surgery† and XRT	Surgery Only
IA	(40)‖	8	1	31
IB	(160)	28	16	116
IIA	(35)‡	34	0	0
IIB	(227)	227	0	0
III	(44)	44	0	0
IV	(16)§	15	0	0
U	(10)	0	10	0
	532	356	27	147

* X-ray therapy.
† Surgery.
‡ 1 Patient died during treatment and is excluded.
§ 1 Patient treated with chemotherapy alone.
‖ In parentheses = no. of patients.

TABLE IV

RECURRENCES

Stage	Pelvis Only	Distant Only	Pelvis and Distant	Total
I Surgery*	2	0	2	4/147
I Surgery and XRT†	1	1	5	7/17
I XRT	1	0	2	3/36
IIA	1	0	1	2/34
IIB	34	23	15	72/227
III	16	4	13	33/44
IV‡	—	—	—	(15/15)
U	0	2	0	2/10
Total	55	30	38	138/530

* Surgery.
† X-ray therapy.
‡ Palliative intent or only symptomatic metastases treated.

1 patient was explored but not resected because of technical difficulties (Table II). The remaining 383 patients, Stages IIA–U, were treated with external beam and 1 or 2 intracavitary applications (Table III). Eleven additional patients were excluded from the tables showing correlation of control and complications because adequate dosimetry information was unavailable or the charts were lost.

Of the 532 patients seen, 137 had persistent disease or developed recurrence. Of the 368 treated with irradiation with curative intent, there were 128 recurrences. The site of recurrence in each stage is shown in Table IV. The time from diagnosis to recurrence is given in Table V and shows that patients with a small volume of tumor initially may take many months for a recurrence to appear.

The probability of controlling the pelvis as a function of ret dose is shown in Table VI. Comparison with the Manchester system using total rads to Point A can be made in Table VII and comparison with the Paris system of combining rads and mgh as a predictor of control can be made in Table VIII.

The ability of the 3 systems to predict the likelihood of a complication can be seen in Tables IX–XI. Figure 1 displays graphically the comparison of the 3 systems for Stage II, for which significant patient numbers were available. Treatment combinations of external beam and intracavitary irradiation correlated with control and complications are presented in Table XII.

TABLE III

XRT TREATMENT COMBINATIONS

Stage	E.B.* Only	1 I.A.†	2 I.A.
I Surgery and XRT‡	15	2	0
I XRT	4	10	22
IIA	1	13	20
IIB	18	73	136
III	30	12	2
IV	13	1	1
U	9	1	0
Total	90	112	181

* External beam.
† Intracavitary application.
‡ Surgery and x-ray therapy.

TABLE V

TIME FOR 90 PER CENT OF RECURRENCES TO APPEAR

Stage	Months
I	38
II	56
III	28
IV	11
Total	40

TABLE VI

PELVIC CONTROL

POINT A RETS

Stage	1,001 2,000	2,001 2,500	2,501 3,000	3,001 3,500	3,501 4,500
I XRT†	5/5 (100)*	5/5 (100)	16/18 (89)	5/5 (100)	2/2 (100)
II	12/21 (57)	28/39 (72)	108/125 (86)	33/40 (83)	24/27 (89)
III	11/32 (34)	1/4 (25)	2/5 (40)	2/3 (66)	—
U	10/10 (100)	—	—	—	—

* In parentheses = percentage.
† X-ray therapy.

TABLE VII

PELVIC CONTROL

POINT A TOTAL RADS

Stage	4,000 5,999	6,000 6,999	7,000 7,999	8,000 8,999	9,000 —
I XRT†	3/3 (100)*	12/12 (100)	10/12 (83)	6/6 (100)	2/2 (100)
II	9/16 (56)	40/51 (78)	73/86 (85)	56/68 (82)	27/31 (87)
III	1/5 (20)	10/27 (37)	3/8 (37)	1/2 (50)	1/2 (50)
U	5/5 (100)	5/5 (100)	—	—	—

* In parentheses = percentage.
† X-ray therapy.

TABLE VIII

PELVIC CONTROL

POINT A RADS + MGH

Stage	3,000 5,999	6,000 6,999	7,000 7,999	8,000 8,999	9,000 —
I XRT†	2/2 (100)*	4/4 (100)	14/15 (93)	7/7 (100)	6/7 (86)
II	7/11 (64)	37/48 (77)	60/70 (86)	53/66 (80)	48/57 (84)
III	1/5 (20)	10/27 (37)	2/5 (40)	3/5 (40)	0/2 —
U	4/4 (100)	6/6 (100)	—	—	—

* In parentheses = percentage.
† X-ray therapy.
MGH = Milligram-hours.

TABLE IX

COMPLICATIONS

POINT A RETS

Stage	1,001 2,000	2,001 2,500	2,501 3,000	3,001 3,500	3,501 4,500
I XRT†	2/5 (40)*	0/5 —	4/18 (22)	0/5 —	0/2 —
II	1/21 (5)	9/39 (23)	18/125 (14)	5/40 (13)	1/27 (4)
III	3/32 (9)	1/4 (25)	1/5 (20)	0/3 —	—
U	2/10 (20)	—	—	—	—

* In parentheses = percentage.
† X-ray therapy.

TABLE X

COMPLICATIONS

POINT A TOTAL RADS

Stage	4,000 5,999	6,000 6,999	7,000 7,999	8,000 8,999	9,000 —
I XRT†	0/3 —	3/12 (25)	3/12 (25)	0/6 —	0/2 —
II	1/16 (6)*	10/51 (20)	12/86 (14)	9/68 (13)	2/31 (6)
III	1/5 (20)	2/27 (7)	2/8 (25)	0/2 —	0/2 —
U	1/5 (20)	1/5 (20)	—	—	—

* In parentheses = percentage.
† X-ray therapy.

TABLE XI

COMPLICATIONS

POINT A RADS + MGH

Stage	3,000 5,999	6,000 6,999	7,000 7,999	8,000 8,999	9,000 —
I XRT†	0/2 —	1/4 (25)	4/15 (27)	1/7 (14)	0/7 —
II	1/11 (9)*	6/48 (13)	15/70 (21)	9/66 (14)	3/57 (5)
III	1/5 (20)	2/27 (7)	2/5 (20)	0/5 —	0/2 —
U	1/4 (25)	1/6 (17)	—	—	—

* In parentheses = percentage.
† X-ray therapy.
MGH = milligram hour.

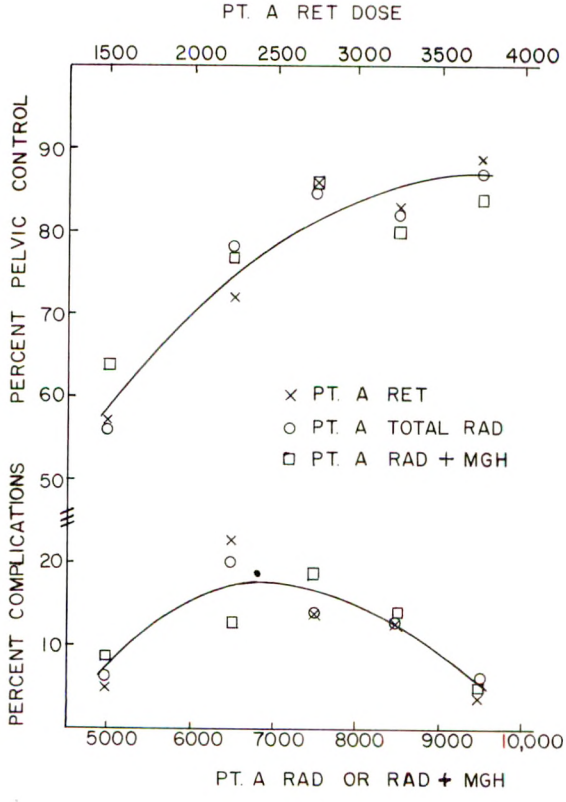

FIG. 1. The upper curve demonstrates per cent pelvic control as a function of Point A ret dose, or Point A total rads, or Point A rads plus milligram hours. The lower curve depicts per cent complications as a function of the same dose schemes. The plot is for Stage II cancer of the cervix.

DISCUSSION

Holthusen (1936)[7] and Strandqvist (1944)[13] developed the concept that tumor control is a function of dose and that the limiting factor in treatment is the probability of complication that accompanies high dose radiotherapy. The 2 dose prescribing systems currently widely used seek to maximize tumor control with acceptable morbidity.

Ellis's application of the NSD concept to the treatment of cervical cancer suggests that a better estimate of probability of control and complication might be available. The analysis of our patient material using the 3 systems fails to confirm that one

TABLE XII

TREATMENT COMBINATIONS RELATED TO PELVIC CONTROL AND COMPLICATIONS

Stage	E.B.* Only	1 I.A.† 2,000–4,000 mgh	2 I.A. 4,000– mgh
I XRT Treated‡	4	10	22
Pelvic Recurrence§	0 —	0 —	2 (9)
Complication‖	1 (25)¶	2 (20)	3 (14)
IIA Treated	1	13	20
Pelvic Recurrence	0 —	0 —	2 (10)
Complication	1 (100)	3 (23)	2 (10)
IIB Treated	18	73	136
Pelvic Recurrence	8 (44)	18 (25)	19 (14)
Complication	0 —	9 (12)	19 (14)
III Treated	30	12	2
Pelvic Recurrence	21 (70)	6 (25)	1 (50)
Complication	3 (10)	9 (12)	1 (50)
IV Treated	13	1	1
Pelvic Recurrence	13 (100)	1 (100)	1 (100)
Complication	1 (8)	0 —	0 —
U Treated	9	1	0
Pelvic Recurrence	0 —	0 —	0 —
Complication	2 (22)	0 —	0 —

* External Beam.
† Intracavitary application.
‡ X-ray therapy.
§ Recurrence.
‖ Complication.
¶ In parentheses = percentage.

system is superior to another as a predictor of pelvic control. All 3 systems show an increase in control as a function of dose.

Furthermore, the 3 systems appear to correlate similarly with the likelihood of developing a complication. It is a surprise that a lower complication incidence is seen at the higher dose range with all 3 predicting systems. It is generally recognized that high dose therapy leads to more complications. Since it is not possible to determine a correlation of increased complication when intracavitary or external beam therapy is emphasized, we believe that other factors are important.

Buchler *et al.*[1] found a significant correlation between Point A ret dose and likelihood of complication which was not noted when they analyzed their material using the Manchester system.[8,13] However, replotting their data on the basis of total rets without regard to whether 1 or 2 applications were used, we note that the percentage of complications is a constant 23 per cent over the range 2,000–5,000 rets. At very high ret doses, 5,000–7,000 rets, the complication rate climbs significantly to 33 to 39 per cent, respectively. None of our patients had ret doses greater than 5,000. A ret dose greater than 5,000 translates to a dose greater than 10,000 rads to Point A.

Other workers have noted an apparent lack of correlation of high dose and incidence of injury.[13] However, there are reports[6,9] which show radiation injury related to dose rate of the intracavitary applicator. These authors indicate that a

history of previous pelvic surgery, retroverted uterus, and narrow vaginal vault probably predispose to injury. The extent of underlying disease is by some authors[15] noted to be a contributing factor but such a trend is not seen among our patients.

It is not possible to identify factors such as emphasis on radium treatment, extent of disease, or dose rate as predisposing factors. In this retrospective analysis it was impossible to identify the proximity of the applicator to bladder, bowel, ureter and sigmoid colon and the temporal relationship to the acute reaction of the external beam regimen.

It may be possible in a prospective manner to determine the influence of dose rate and integral dose on complications. The versatility of afterloading applicators and convenience of computer dosimetry allow determining dose to bladder wall, rectum, sigmoid and the minimal and maximal doses within a tumor volume. With the technology now available, treatment can be prescribed in terms of rads to a defined tumor volume rather than to artificial points such as A and B or employing a quasi-dose such as mgh.

SUMMARY

The use of 3 dose assessment systems is compared.

The Manchester approach which measures a dose to Point A and Point B; the Paris approach using rads and mgh; and Ellis's NSD approach appear to have equal value in predicting probability of pelvic control and the likelihood of complication over the dose range employed at this hospital.

Control increases with higher dose schemes, but complications appear to be influenced by other variables not accounted for in the 3 systems.

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INDICATIONS FOR ADJUNCTIVE CONSERVATIVE EXTRAFASCIAL HYSTERECTOMY IN SELECTED CASES OF CARCINOMA OF THE UTERINE CERVIX*

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SINCE 1954 there has been an increased use of adjunctive conservative extrafascial hysterectomy added to slightly diminished irradiation, either because of the bulk of the central lesion or other indications not related to the growth pattern of the disease.

Two hundred and twelve patients with either squamous cell or adenocarcinoma have had this modality of treatment with a minimum of 5 years follow-up.

The modifications in radiation techniques, the results in both survival rates and sites of failures, and complications will be reviewed. From this analysis, clear guidelines can be given as to in which situations this combined modality is preferable to radiation therapy alone, with a better definition of the radiation therapy which can be safely given.

An analysis by Durrance *et al.*[1] of the results in 1,341 Stages I and II squamous cell carcinomas of the cervix treated at M. D. Anderson Hospital from 1948 through 1963 showed that there were few central recurrences in Stage I. In Stage II, most central recurrences developed in those patients with bulky, usually barrel-shaped endocervical lesions.[1] When, for these large lesions, an extrafascial conservative hysterectomy was added to slightly less radical radiotherapy, the central recurrence rate in this selected group of patients was reduced from 15 to 3 per cent.[2] This notable improvement in the control of central disease by the addition of the conservative operation 4 to 6 weeks after completion of radiotherapy with a relatively low incidence of severe complications encouraged its continued use at this institution.[6] The present essay is a review of the M. D. Anderson Hospital experience with this combined radiotherapeutic and surgical approach.*

SUBSTAGING OF CARCINOMA OF THE CERVIX

When megavoltage equipment (particularly the 22 MeV beam) became available in 1954, the opportunity to use high-dose whole pelvis irradiation led to its use in increasing doses for increasing volume of cancer prior to intracavitary radium therapy.

It was believed that in the Stage II cases when the central mass was more than 6 cm. in diameter, *i.e.*, more than half the diameter of the pelvis, initial intracavitary gamma ray therapy would be ineffective. The purpose of starting with whole pelvis irradiation was to shrink the disease prior to intracavitary radium therapy. It led to a subdivision of the International Staging System relating volume of cancer with prognosis and treatment planning (Fig. 1). This substaging has been kept, after FIGO changes, because it fits clinical realities with therapeutic consequences.

CLINICAL MATERIAL AND METHODS

From September 1, 1954, through December 31, 1967, 212 patients with either squamous cell carcinoma or adenocar-

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From the University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute at Houston, Houston, Texas.

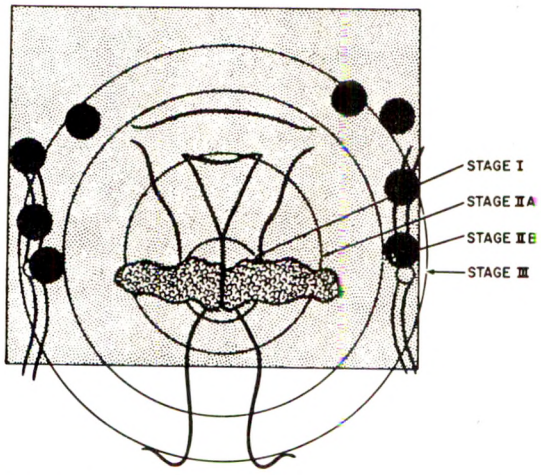

FIG. 1. Stage IIA. Spread to upper two-thirds of vagina and/or medial parametria. Stage IIB. Lateral parametrial involvement (with or without upper vaginal extension) or massive involvement of the corpus; in this latter growth pattern, the parametria cannot be properly evaluated. Stage IIIA. Tumor involvement of one pelvic wall or of lower third of vagina. Stage IIIB. Spread to both pelvic walls or to one wall and lower third of vagina. Stage IV. Invasion of bladder or rectum and/or distant metastases. (Reproduced with permission from: G. H. Fletcher, *Textbook of Radiotherapy*. Second Edition. Lea & Febiger, Philadelphia, 1973.)

cinoma of the uterine cervix were treated by combining slightly less than radical radiotherapy with a conservative extrafascial hysterectomy. During the first years of this period, lymphadenectomy or multiple lymph node biopsies were also done.

The indications for hysterectomy are listed in Table 1 by stage and histology. In both histologic groups, the presence of bulky or barrel-shaped endocervical disease has been the main indication for hysterectomy, since adequate irradiation cannot be given (Fig. 2, *A* and *B*). Most adenocarcinomas grow endocervically, and squamous cell cancer frequently also grows predominantly endocervically, invading and enlarging the lower uterine segment to create a barrel-shaped lesion. The diagnosis of adenocarcinoma was the indication for surgery in 22 Stage I and 6 Stage IIA patients because of the prevailing opinion held in the past that adenocarcinoma is less radiosensitive than squamous cell carcinoma. Other indications for hysterectomy were pregnancy, incomplete radiation therapy because the internal os could not be found, positive endometrial biopsy, and the presence of uterine fibroids, etc.

Evaluation of the status of the parametria in the presence of a large central mass is difficult. Central masses 6 cm. or more (sometimes 8 to 10 cm.) close to both pelvic walls but still movable, do not allow an adequate rectal palpation of the parametria and a clear separation between an expanded uterus and parametrial infiltration. A better evaluation of the parametria can be done after 4,000 rads whole pelvis irradiation because there is usually some diminution of the size of the central mass.

On initial examination in the GYN Disposition Clinic, a tentative plan is made to add the hysterectomy. The decision to carry on with the procedure is made after 4,000 rads whole pelvis irradiation, since by then the status of the parametria is better appreciated (Fig. 3).

If the parametria are free of disease, a 72 hour radium application is done with the intrauterine tandem loaded 15-15-10 mg. and the vaginal ovoids loaded according to their size.[3] The 4,000 rads external irradiation of the whole pelvis and the 5,000 mg.-hr. radium application deliver a total of 8,000–10,000 rads surface dose to the vaginal mucosa and 5,000 rads to the lateral parametria, obturator, and external iliac lymph nodes (Fig. 3). Six weeks later a conservative extrafascial hysterectomy is performed.

If after 4,000 rads whole pelvis irradiation there is still definite parametrial disease, a conservative hysterectomy would be inappropriate since it would cut through gross disease. In these patients, a 48 hour application of tandem and ovoids loaded as above is followed in 2 to 3 weeks by a second 48 hour insertion of an intrauterine tandem alone. If after an additional 2 to 3 weeks of rest the central disease is still palpable, a third insertion of tandem only is done. This insertion is for 24 hours. The

TABLE I

INDICATIONS FOR HYSTERECTOMY BY STAGE AND HISTOLOGY
(ADENOCARCINOMA AND SQUAMOUS CELL CARCINOMA)

(September 1, 1954—December 31, 1967)
(Analysis July, 1973)

ADENOCARCINOMA

Stage	No. of Patients	Bulky or Endocervix Barrel-shaped	Pregnancy	Incomplete Treatment	Other: Fibroid, etc.	Adenocarcinoma
I	33	9	2			22
IIA	17	9			2	6
IIB	14	12	1		1	
IIIA	4	4				
IIIB	1	1				
IV						
Total	69	35	3		3	28

SQUAMOUS CELL CARCINOMA

Stage	No. of Patients	Bulky or Endocervix Barrel-shaped	Pregnancy	Incomplete Treatment	Other: Fibroid, etc.	Endometrium Positive
I	28	17	3	2	3	3
IIA	18	13	2	1	2	
IIB	74	73			1	
IIIA	16	15				1
IIIB	6	6				
IV	1*	1				
Total	143	125	5	3	6	4

* Unrecognized distant metastasis present at time of surgery.

emphasis on the intrauterine tandem expands the usual pear-shaped isodose curves to encompass more of the myometrium. This technique delivers 7,000–8,000 rads surface dose to the vaginal mucosa and 5,000–5,500 rads to the lateral parametria, obturator, and external iliac lymph nodes (Fig. 2, *A* and *B*).

When the status of the parametria is in doubt after 4,000 rads whole pelvis irradiation, a 72 hour radium insertion is followed by exploratory laparotomy. If the parametria are found to be free of disease, the conservative hysterectomy is done. If parametrial disease is present, the abdomen is closed and additional intrauterine radium insertions are given.

If, in selected Stage III patients with large central lesions, the parametria have become soft after 4,000 or 5,000 rads whole pelvis irradiation and there is still a large central mass, an exploratory procedure is performed; if parametria are free on palpation, an appropriate and less-than-radical hysterectomy is performed.[7]

SURVIVAL RATES AND SITES OF FAILURES

The 5 year survival rates by stage and histology are given in Table II. The survival rates are comparable to those for carcinoma of the cervix in general, which is gratifying in a group of patients with extensive disease.[5] It must be mentioned that

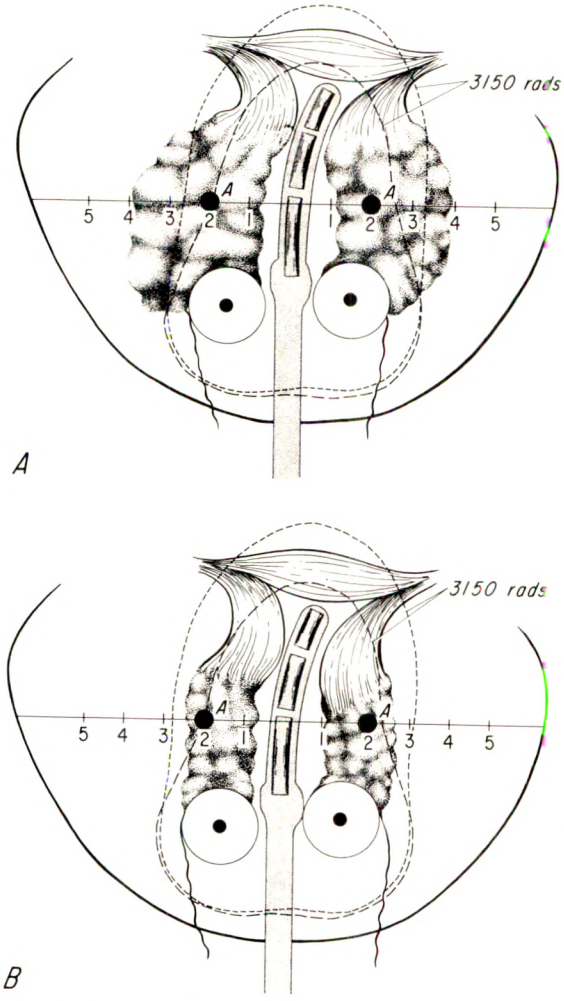

FIG. 2. (*A*) In the bulky, barrel-shaped endocervical lesions, tumor cells deep in the myometrium are outside the zone of adequate irradiation. The inner interrupted line is the pear-shaped 3,150 rad isodose curve which resulted from one 72 hour insertion of a radium system, consisting of a tandem loaded 15-15-10 mg. and small ovoids loaded 15-15 mg. This radium application and the 4,000 rads external irradiation of the whole pelvis deliver 8,000–10,000 rads surface dose to the vaginal mucosa and 5,000 rads to the lateral parametria, obturator, and external iliac lymph nodes. The outer dotted line shows that the 3,150 rad isodose curve can be expanded to include more of the myometrium by using 3 radium insertions. The first is a 48 hour application of tandem and ovoids loaded as above. The second and third insertions employ only the tandem loaded with 15-15-10 mg. for 48 and 24 hours, respectively. This technique delivers 7,000–8,000 rads surface dose to the vaginal mucosa and 5,000–5,500 rads to the lateral parametria, obturator, and external iliac lymph nodes. Two to 3 weeks are allowed between radium insertions to allow regression of the disease. Neither of these isodose distributions encompasses the disease when its diameter exceeds 5–6 cm. (*B*) After 4,000 rads whole pelvis irradiation, the central disease may shrink sufficiently to permit adequate irradiation by emphasizing the intrauterine radium and properly fractionating the applications as described above. It should be pointed out that Point A is still within the disease after shrinkage.

the average age of the patients in this study is 46.7 years compared with 53 years for all patients with squamous cell carcinoma of the cervix. Therefore, part of these good survival rates results from the fact that the patients are young and must be in good general condition to be suitable for the surgical procedure.

The sites of active disease at the time of death for squamous cell and adenocarcinoma patients dying before or after 5 years are shown in Tables III and IV.

COMPLICATIONS

Table V relates the incidence of severe and fatal complications to the dose levels of whole pelvis irradiation. The incidence of severe complications when whole pelvis irradiation was 4,000 rads or less was 5.4 per cent, whereas 2 of 3 patients who had more than 4,000 rads whole pelvis irradiation had severe complications.

From 1954 to 1962, pelvic lymphadenectomies were performed in this institution as part of a study of the effectiveness of radiation on lymph nodal metastases from carcinoma of the cervix. In addition to demonstrating that pelvic node metastasis can be sterilized by radiotherapy and that lymphadenectomy does not improve the cure rate, this investigation revealed a high incidence of complications related to lymphadenectomy (Table VI).[7] At all dose levels, the complication rate is at least doubled by the addition of lymphadenectomy. There were 4 fatal complications in the lymphadenectomy group and no fatalities in the absence of this procedure.

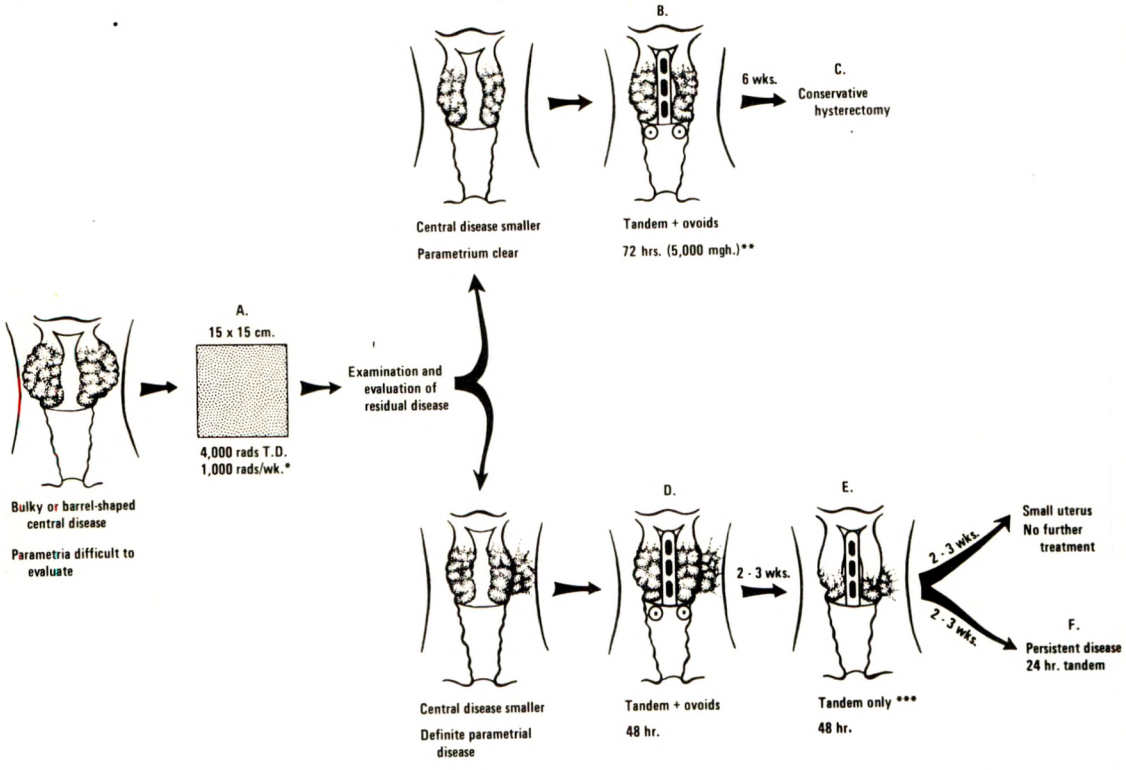

FIG. 3. * Transvaginal irradiation (500 rads daily twice or three times) may be given first for hemostasis and accelerated shrinkage of the friable component of the tumor. This dosage is generally disregarded in further treatment planning. ** Phases A and B deliver 8,000–10,000 rads to the vaginal mucosa, at least 7,000 rads to the paracervical lymphatics, and 5,000 rads to the lateral parametria, obturator, and external iliac lymph nodes. The tandem is loaded with 15–15–10 mg. and the ovoids according to their size. *** Phase D. The tandem is loaded 15–15–10 mg. and the ovoids according to their size. After the second radium insertion (E) the patient has received 5,280 mg.-hr. After the third radium application (F) the total mg.-hr. is 6,240. Note that vaginal radium is used only in the first insertion.

Among 95 patients treated by radiotherapy and conservative hysterectomy only, 7 had severe complications. Six of these patients had either vesico- or recto-vaginal fistulae. For carcinoma of the cervix in general, the probability of fistula formation is increased with bulky central disease, extensive vaginal involvement, whole pelvis irradiation above 4,000 rads and the use of compact, heavily loaded radium systems.

One patient had a small bowel obstruction. This patient had a history of previous abdominal surgery and received 5,000 rads whole pelvis irradiation. When this complication has occurred, there has usually been a history of previous abdominal surgery or perforation of the uterus at the time of radium insertion. Small bowel loops receive high doses of irradiation when bound to the uterus by adhesions.[3,8] While bowel complications can result from either radiotherapy or surgery, it is not usually possible in these cases to place the blame on either when both modalities of treatment are used. It is known from our experience with patients treated by radiotherapy alone that radionecrosis of the small bowel is infrequent with whole pelvis irradiation doses of 4,000 rads or less.

DISCUSSION

A bulky, usually barrel-shaped endocervical lesion is the principal indication for combining radiotherapy and conservative extrafascial hysterectomy. The ra-

Table II

5 YEAR SURVIVAL RATES ACCORDING TO STAGE AND HISTOLOGY
(September 1, 1954–December 31, 1967)
(Analysis July, 1973)

5 YEAR SURVIVAL: ADENOCARCINOMA

Stage	No. of Patients	NED	Alive With Disease	Absolute Survival	Determinate Survival
I	33	27		82% (27/33)	87%*
IIA	17	10		59% (10/17)	63%
IIB	14	8		57% (8/14)	57%
IIIA	4	4		100% (4/4)	100%
IIIB	1	1		100% (1/1)	100%
Total	69	50		72% (50/69)	76%

5 YEAR SURVIVAL: SQUAMOUS CELL CARCINOMA

Stage	No. of Patients	NED	Alive With Disease	Absolute Survival	Determinate Survival
I	28	26		93% (26/28)	93%
IIA	18	15	1	89% (16/18)	94%†
IIB	74	55	1	76% (56/74)	79%
IIIA	16	6		38% (6/16)	43%
IIIB	6	2		33% (2/6)	33%
IV	1			(0/1)	
Total	143	104	2	74% (106/143)	77%

* Excluding 2 Stage 1 patients who died of unknown causes at 7 and 17 months.
† Excluding 1 patient who died at 21 months of unknown causes.
NED= no evidence of disease.

Table III

SQUAMOUS CELL CARCINOMA
STATUS OF DISEASE AT TIME OF DEATH IN PATIENTS DYING BEFORE 5 YEARS
(September 1, 1954–December 31, 1967)
(143 Patients)
(Analysis July, 1973)

Stage	No. of Patients Treated	Central	Reg.	Central + Reg.	Central + DM	Reg. + DM	Central + Reg. + DM	DM	Comp.	ID	No Data	Total
I	28		1			1		1				3
IIA	18							1			1	2
IIB	74		4			2		10	1	4		21
IIIA	16	3	1			1		2	1	2		10
IIIB	6			1					2	1		4
IV	1							1				1
Total	143	3	6	1		4		15	4	7	1	41

Of the squamous cell carcinoma patients dying after 5 years, there were no central recurrences. One patient died of combined regiona and distant metastatic disease, 3 of distant metastases without central or regional disease, and 10 of intercurrent disease.
Definitions:
Central —clinical or biopsy evidence of persistent or recurrent disease either on the cervix, in the body of the uterus, or in the upper two-thirds of the vagina.
Regional—disease anywhere in the pelvic structures or in regional lymphatics, including common iliac lymph nodes.
Abbreviations: Reg.—regional disease; DM—distant metastases; ID—intercurrent disease; Comp.—complications.

TABLE IV

ADENOCARCINOMA
STATUS OF DISEASE AT TIME OF DEATH IN PATIENTS DYING BEFORE 5 YEARS
(September 1, 1954–December 31, 1967)
(69 Patients)
(Analysis July, 1973)

Stage	No. of Patients Treated	Central	Reg.	Central + Reg.	Central + DM	Reg. + DM	Central +Reg. +DM	DM	Comp.	ID	No Data	Total
I	33		2	1					1		2	6
IIA	17	1	1			1		3		1		7
IIB	14		1	2				5				8
IIIA	4											
IIIB	1											
Total	69	1	4	3		1		8	1	1	2	21

The adenocarcinoma patients died after 5 years of central recurrence in 1 case, distant metastases in another, complications in another, and intercurrent disease in 3 cases. In 1 patient the cause of death is unknown.

Definitions:

Central —clinical or biopsy evidence of persistent or recurrent disease either on the cervix, in the body of the uterus, or in the upper two-thirds of the vagina.

Regional—disease anywhere in the pelvic structures or in regional lymphatics, including common iliac lymph nodes.

Abbreviations: Reg.—regional disease; DM—distant metastases; ID—intercurrent disease; Comp.—complications.

tionale is that the hysterectomy removes disease in the myometrium which is too far from the radium system to receive an effective dose, whereas irradiation is adequate for the amount of disease in the parametria and vaginal mucosa.[2–4] Central failures have been almost entirely eliminated.

The diagnosis of adenocarcinoma is no longer considered *per se* a sufficient indication for the addition of a hysterectomy. When the volume of cancer is the same, adenocarcinoma is as well controlled by radiotherapy as is squamous cell carcinoma.

The geometry of a large central carcinoma of the cervix is such that maximum intracavitary radium, emphasizing uterine radium, must be used when a hysterectomy is not performed (Fig. 2, *A* and *B*). This radical irradiation may precipitate the development of a sigmoiditis (Fig. 4). The combination of irradiation and an extrafascial conservative hysterectomy without lymphadenectomy is an alternative approach accompanied by less severe complications.

TABLE V

SEVERE COMPLICATIONS RELATED TO DOSE LEVEL OF EXTERNAL BEAM WHOLE PELVIS (WP) IRRADIATION IN PATIENTS TREATED BY RADIATION THERAPY+CONSERVATIVE HYSTERECTOMY
(Analysis July, 1973)

Treatment	Fistulae	Sigmoiditis	Small Bowel Obstruction	Fatal Complications	Total†
<4000 WP	5/68*	0	0	0	5/68
4000 WP	0/24	0	0	0	0/24
>4000 WP	1/3	0	1/3	0	2/3

* Sigmoidovaginal fistula in 1 patient whose sigmoid was accidentally lacerated at surgery.

† Complication rate when whole pelvis irradiation was 4,000 rads or less was 5.4 per cent, 2 out of 3 patients who had >4,000 rads WP had severe complications.

TABLE VI

COMPLICATIONS
COMBINED CONSERVATIVE HYSTERECTOMY AND IRRADIATION

(September 1, 1954–December 31, 1967)
(Analysis July, 1973)

	XRT+Hyst.+Lymph.	XRT+Hyst.
All Complications*	29/80 (36.3%)	14/95 (14.7%)
Fistulae	7	6
Sigmoiditis	2	0
Small Bowel Obstruction	3	1
Fatal Complications	4	0
Total Severe Complications†	14/80 (17.5%)‡	7/95 (7.4%)

* All recorded complications.

† Severe complications as specifically listed. This does not include the lymphocysts which were common in the lymphadenectomy group.

‡ Two patients who had fistulae and ultimately died of complications are listed under fistulae and under fatal complications but are not counted twice in computing the total number of severe complications.

Abbreviations: XRT—Irradiation; Hyst.—Extrafascial conservative hysterectomy; Lymph.—Lymphadenectomy.

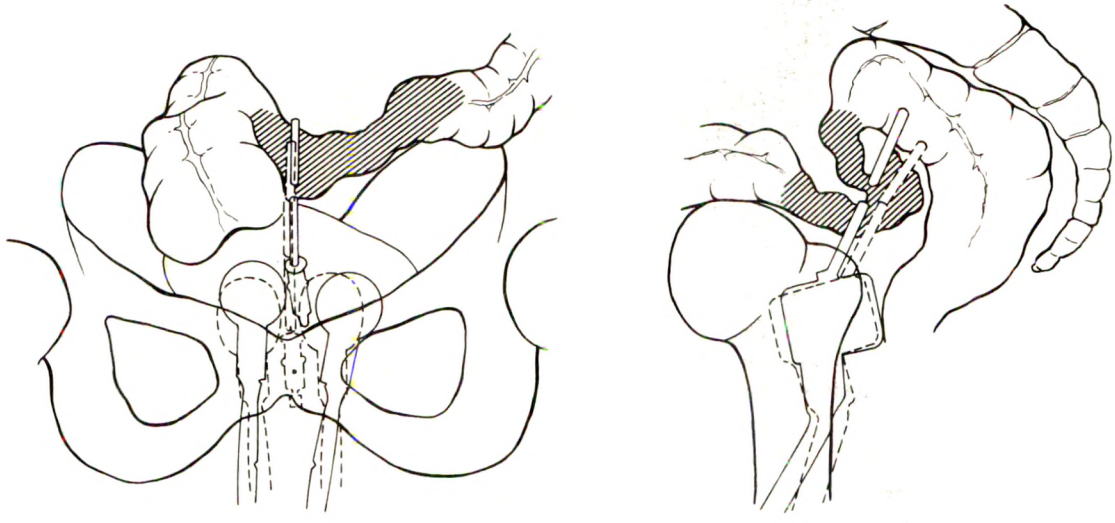

FIG. 4. Tracings of anteroposterior and lateral roentgenograms. The patient, age 58, had squamous cell carcinoma of the endocervix producing a barrel-shaped mass more than 6 cm. in diameter. There was also positive endometrial biopsy and shortening of the right parametrium. The patient first received 4,000 rads in 4 weeks through 2 parallel opposing portals, 15×15 cm., with the 22 MeV beam. The patient then had 2 radium applications, the first with a tandem 15–15–6 mg. and 2 small ovoids 15–15 mg. left for 30 hours, and the second application 1 week later with a tandem 15–15 mg. and small ovoids 10–10 mg. left for 72 hours. The total of mg.-hr. was 5,580. The treatment was completed on November 17, 1961. On September 11, 1962, the patient was admitted with possible bowel obstruction, with bloody discharge from the rectum. Barium enema examination showed a lesion in the loops of sigmoid. On December 4, 1962, there was improvement of symptoms; on March 5, 1963, there was evidence of a rectal ulcer 6 cm. inside the anal opening. Until 1964, the patient had some inconvenience with episodes of diarrhea and constipation and occasional bleeding. From 1965 until April 30, 1968, the patient was completely asymptomatic. Diffuse intense fibrosis in both parametria is the only finding on palpation. (Courtesy: Strockbine, *et al.*, AM. J. ROENTGENOL., RAD. THERAPY & NUCLEAR MED., 1970, *108*, 293.)

SUMMARY

The survival rates for a selected group of patients with large central lesions, either squamous cell carcinoma or adenocarcinoma and managed by combining irradiation and a conservative extrafascial hysterectomy, are comparable to those of carcinoma of the cervix in general.

Death is caused much more often by distant metastases and intercurrent disease than by failure within the irradiated volume.

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ARTERIOGRAPHIC DEMONSTRATION OF INTRAVENOUS TUMOR EXTENSION*

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KAHN[3] and Ferris *et al.*[2] described a linear striated vascular pattern on selective renal angiography, indicating extension of renal carcinoma into the renal vein and the inferior vena cava. There has been no description of this angiographic appearance with intravascular invading neoplasms other than hypernephroma reported in the literature.

The present communication further emphasizes this characteristic striated arterial pattern as reliable evidence of intravenous neoplastic extension in other than renal tumors. The patients with this angiographic phenomenon described in this report had primary hepatocellular carcinomas and retroperitoneal soft tissue osteosarcoma.

REPORT OF CASES

CASE I. A 22 year old male was evaluated for a right lower quadrant abdominal mass associated with a 1 month history of right lower extremity edema and a right foot drop. Abdominal roentgenograms demonstrated a 6×6 cm. calcified mass adjacent to the right lumbosacral region. Intravenous urography showed anterior displacement of the mid-right ureter, and lymphangiography demonstrated lymph node displacement in this region. Lumbosacral tomography demonstrated no bone destruction in association with the calcified mass. Lumbar myelography revealed a right-sided extradural defect at the L_4–L_5 level.

Abdominal aortography disclosed a remarkable appearance of numerous parallel arterial channels located in the expected anatomic position of the inferior vena cava, extending from the lumbosacral area to the medial aspect of the right hemidiaphragm (Fig. 1*A*). Selective injections showed that the vessels arose from multiple lumbar arteries and an enlarged right testicular artery. Venous injections demonstrated total occlusion of the inferior vena cava and right iliac vein with a filling defect in the right atrium.

The patient underwent laminectomy with excision of the extradural tumor and was then placed on chemotherapy.

He expired a short time thereafter, and necropsy rendered the diagnosis of soft tissue osteosarcoma arising adjacent to the right side of the fourth and fifth lumbar vertebrae. There was considerable regional soft tissue extension. The inferior vena cava was dilated to a 6 cm. diameter. Tumor and blood clot were intermixed throughout the entire vena cava with the proximal portion of the tumor protruding into the right atrium and right ventricle (Fig. 1*B*). Massive chronic passive congestion of the liver and ascites were present secondary to obstruction of the inferior vena cava by the tumor. Cross-sectional microscopic examination of the inferior vena cava at numerous levels demonstrated vascular channels both within and adjacent to the caval wall, corresponding in size to the arteries demonstrated by angiography (Fig. 1*C*).

CASE II. An 8 month old male infant was referred for evaluation of abdominal distention and a right upper quadrant abdominal mass. Physical examination revealed a protuberant abdomen with a large, nodular liver.

Hospital evaluation included abdominal arteriography which demonstrated a mass lesion in the superior portion of the right lobe of the liver. Considerable neovascularity was present with several fine linear arteries coursing from the medial aspect of the tumor in the expected direction of the right hepatic vein at its entrance into the inferior vena cava (Fig. 2*A*). Subsequent inferior vena cavogram confirmed massive tumor extension into the vena cava at the level of the diaphragm with virtually total occlusion (Fig. 2*B*).

Paracentesis of ascitic fluid was positive for

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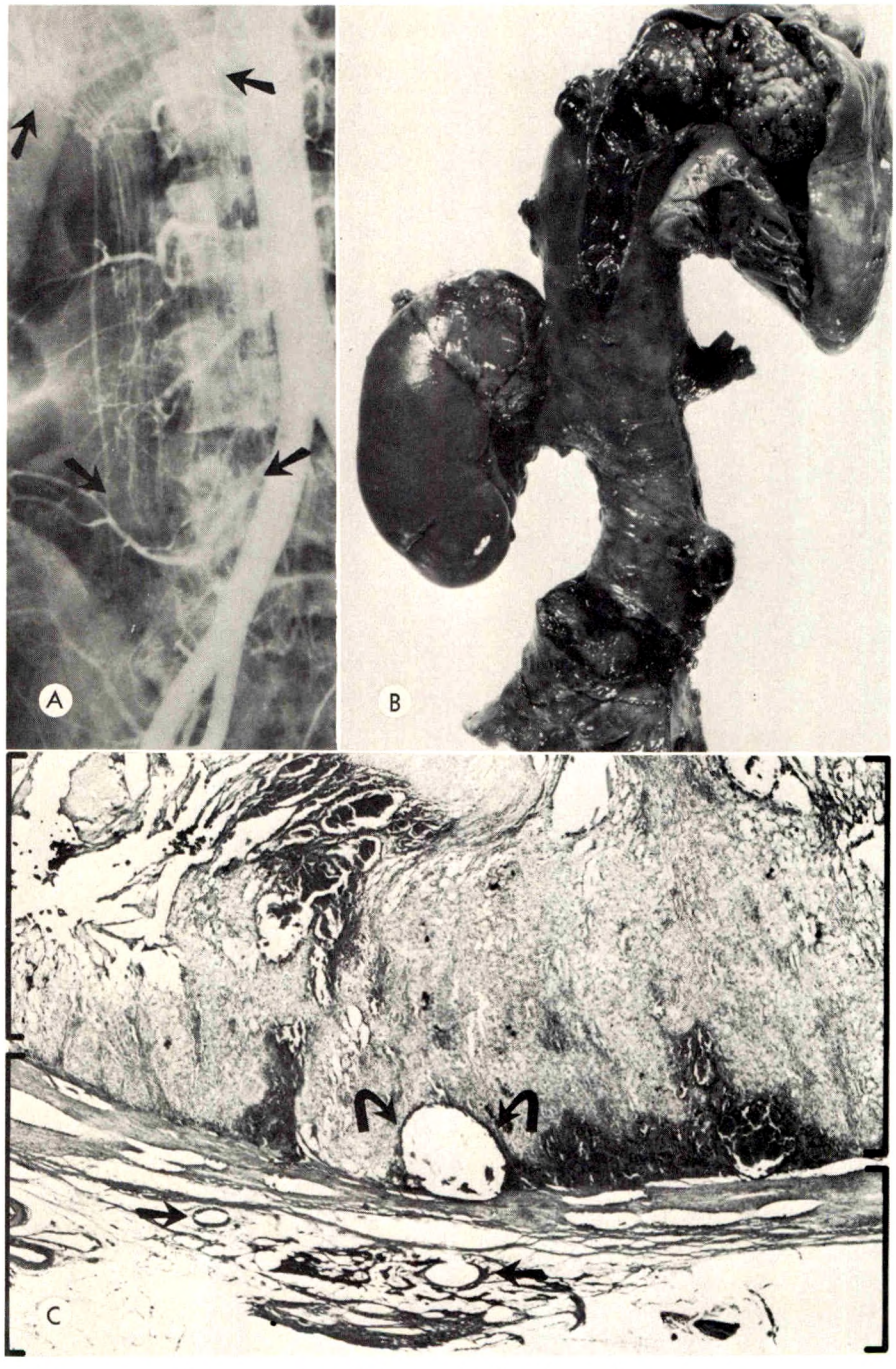

Fig. 1. Case 1. Retroperitoneal osteosarcoma with extension into the entire vena cava.

(*A*) Abdominal aortogram reveals a prominent striated arterial pattern in the anatomic position of the inferior vena cava (arrows). The arteries appear normal. (*B*) Gross specimen demonstrates a massively distended inferior vena cava containing tumor and blood clot. The superior portion of the tumor is protruding into the right heart. (*C*) Enlarged cross-sectional photomicrograph of a portion of the mid-inferior vena cava. The upper brackets delineate the intraluminal tumor and the inferior brackets encompass the caval wall. Several distinct vascular channels are present in the caval wall (straight arrows) including a large subendothelial vessel (curved arrows) corresponding to one of the arteries demonstrated by angiography.

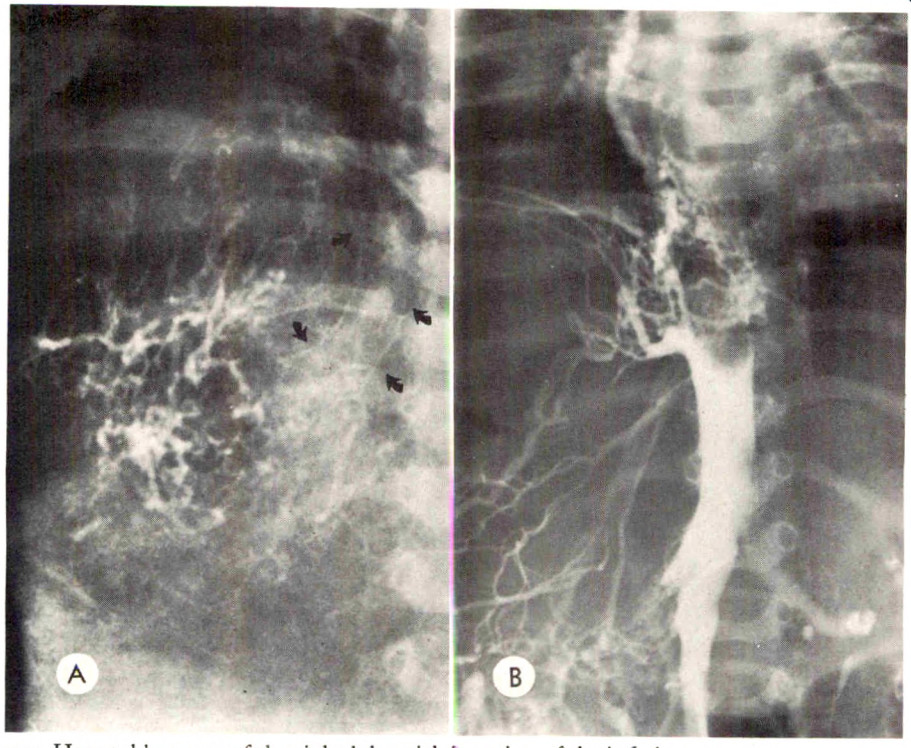

FIG. 2. Case II. Hepatoblastoma of the right lobe with invasion of the inferior vena cava.
(*A*) Parenchymal phase of hepatic arteriogram demonstrating tumor vascularity in the superior portion of the right lobe. Several fine linear arteries (arrows) course from the tumor in the anatomic distribution of the draining right hepatic vein. (*B*) Inferior vena cavogram demonstrates total occlusion of the vena cava by tumor with filling of multiple collateral veins.

malignant cells. The patient was begun on chemotherapy and radiotherapy, but expired 3 months later.

Autopsy confirmed the diagnosis of hepatoblastoma with direct invasion and obstruction of the inferior vena cava. Multiple pulmonary metastases were present as well as chronic passive congestion of the liver, secondary to venous outflow obstruction.

CASE III. A 57 year old female was examined by her local physician for an epigastric mass. A liver scan showed a cold area in the left lobe.

Exploratory laparotomy and liver biopsy revealed diffuse postnecrotic cirrhosis and a hepatoma confined to the left lobe. The patient was subsequently referred for further evaluation and possible partial hepatic resection.

Visceral arteriography demonstrated a hypervascular mass compatible with hepatoma located primarily in the medial segment of the left lobe of the liver. Multiple parallel arterial channels arose from the mass and ran in the anatomic distribution of the middle hepatic vein and inferior vena cava junction with apparent extension into the right atrium (Fig. 3, *A* and *B*). The venous phase of the superior mesenteric arteriogram also demonstrated a large thrombus in the portal vein. Inferior vena cavography confirmed a mass to be partially obstructing the inferior vena cava and protruding into the right atrium (Fig. 3*C*).

Chemotherapy was initiated, but the patient expired shortly thereafter.

DISCUSSION

Clinical symptomatology of intravenous neoplastic extension usually reflects both the type of primary tumor and the anatomic level of venous involvement. One potential clinical manifestation of hepatic vein and/or high inferior vena caval obstruction by tumor is a Budd-Chiari syndrome. Two of our patients (Cases I and II) had considerable passive hepatic con-

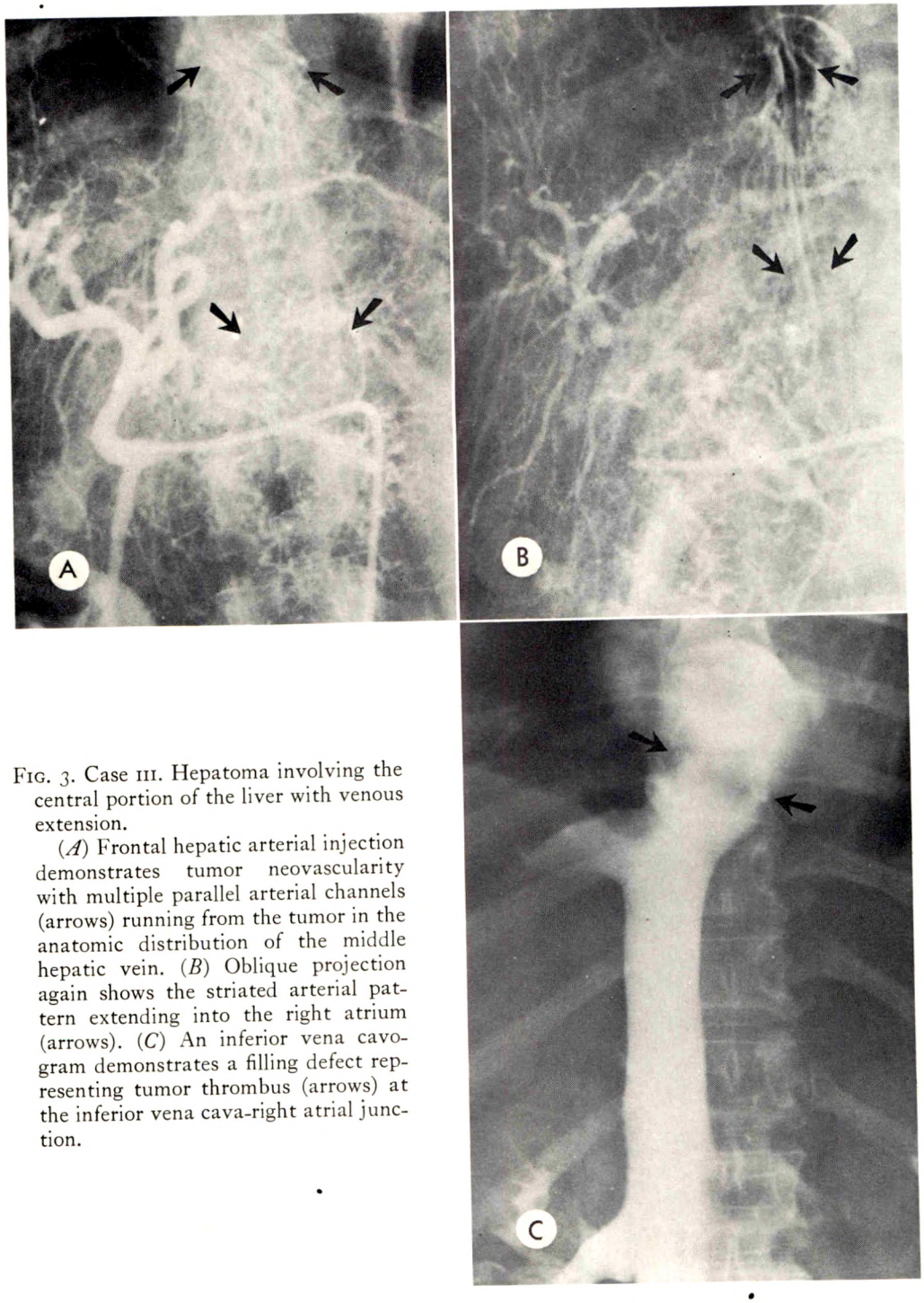

Fig. 3. Case III. Hepatoma involving the central portion of the liver with venous extension.

(*A*) Frontal hepatic arterial injection demonstrates tumor neovascularity with multiple parallel arterial channels (arrows) running from the tumor in the anatomic distribution of the middle hepatic vein. (*B*) Oblique projection again shows the striated arterial pattern extending into the right atrium (arrows). (*C*) An inferior vena cavogram demonstrates a filling defect representing tumor thrombus (arrows) at the inferior vena cava-right atrial junction.

gestion, and Case 1 had nonmalignant ascites as well. Deutsch *et al.*[1] recently described the angiographic examination of a patient with a primary leiomyosarcoma of the inferior vena cava having a similar clinical appearance. Intracardiac extension of such primary or metastatic intracaval tumors may also present a particularly

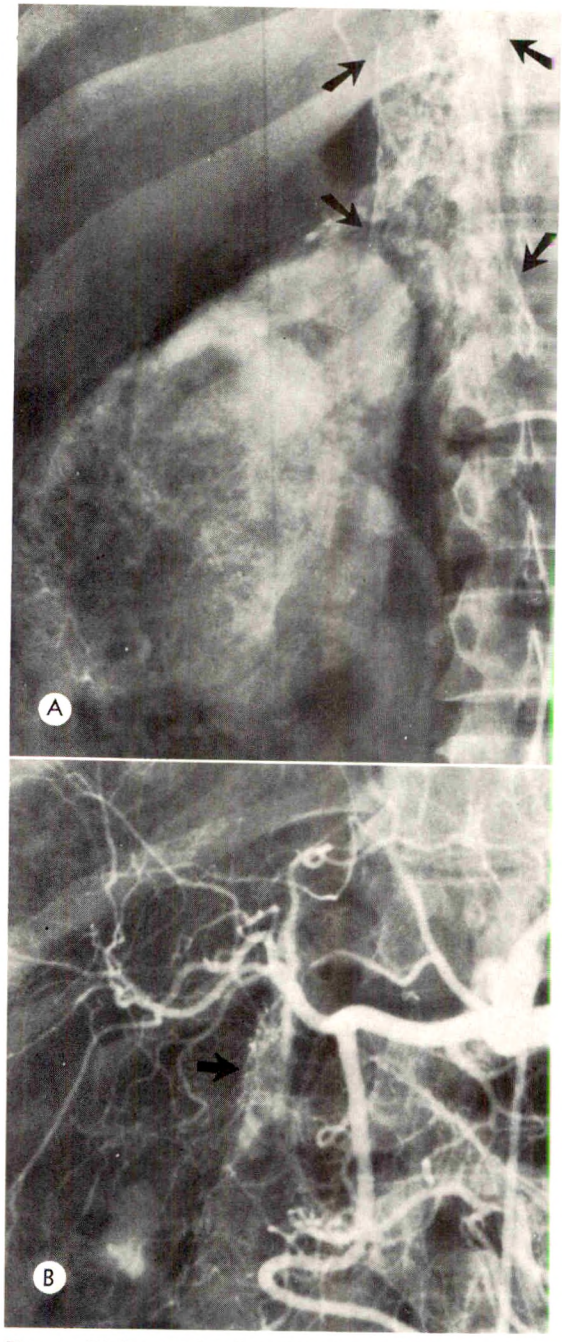

FIG. 4. Right renal cell carcinoma with extension to the inferior vena cava.

(*A*) Right renal arteriogram demonstrates a large hypernephroma with considerable arterial supply to the intracaval tumor extension (arrows). (*B*) Celiac arteriogram also demonstrates tumor vascularity (arrow) arising from the hepatic artery to the intracaval tumor.

confusing clinical picture. For example, atrial extension associated with clinical cardiac symptoms and a filling defect demonstrated on angiocardiography or isotopic study may suggest an atrial myxoma or other primary cardiac tumor. Associated tumor embolization to the lung is an additional sequela which can be misleading.

The arteriographic demonstration of characteristic parallel arterial channels in the anatomic distribution of a vein draining a tumor is reliable evidence of venous extension. Direct venography should always be performed to both confirm this finding and determine the extent of the venous involvement. On the other hand, the venographic differentiation of tumor thrombus from blood clot is often impossible. When present, the striated arterial pattern will facilitate this differentiation.

Renal vein and inferior vena caval extension and/or invasion is a well known complication of renal cell carcinoma.[4] Complete preoperative angiographic evaluation of a hypernephroma includes inferior vena cavography as well as renal vein visualization, if the vena cava is not involved. Similar to renal neoplasms, extension into the inferior vena cava also frequently occurs with malignant hepatocellular tumors.[5] The importance of angiographic investigation of the inferior vena cava in assessing operability of hepatomas is not widely recognized. Inferior vena cavography in the frontal and oblique or lateral projections should be routinely performed in all cases of hepatomas which appear surgically resectable on hepatic arterial study. As in Cases II and III, a tumor apparently confined to a relatively small portion of the liver may be inoperable because of extension into the inferior vena cava.

Virtually all of our cases have been similar in appearance to those described by Kahn[3] and Ferris *et al.*[2] We have most frequently observed the striated vascular pattern with hypernephromas. Most often, the striated pattern appears to be com-

posed of arterial channels which extend directly from the tumor and follow the course of the invaded venous structure. In 1 renal cell carcinoma examined recently, some tumor vascularity supplying the vena caval extension arose from the hepatic artery as well as the tumor (Fig. 4, *A* and *B*). In the patient with retroperitoneal osteosarcoma invading the inferior vena cava, the vessels had an uninterrupted, normal appearance and arose from aortic branches along the course of the vena cava.

Pathologically, the vascular striated appearance represents the arterial supply to the intravenous component of the neoplasm. The location of these arterial channels in all cases is uncertain. Their frequent neovascular appearance suggests that they may be located within the invading tumor substance itself on occasion. However, in Case 1, cross-sectional microscopic examination demonstrated their location both within and adjacent to the caval wall. This observation suggests that the parallel arteries may sometimes represent markedly enlarged vasa vasorum, particularly when they are normal in appearance.

SUMMARY

The arteriographic demonstration of a linear, striated arterial pattern in the anatomic course of the draining vein is reliable evidence of venous extension by a tumor and represents the supply to the intravenous component of the neoplasm.

In addition to its previously described occurrence with hypernephromas, this report documents the characteristic angiographic appearance with hepatocellular tumors and a retroperitoneal osteosarcoma as reliable evidence of tumor extension into the inferior vena cava.

It is possible that in some cases, the parallel arteries represent markedly enlarged vasa vasorum of the involved venous structure.

The frequent invasion of the inferior vena cava by hepatomas and the importance of inferior vena cavography in their angiographic evaluation is also emphasized.

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LYMPHANGIOGRAPHY IN OVARIAN CANCER*

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CARCINOMA of the ovary is the fourth most frequent cause of female cancer deaths in the United States and the leading cause of death among gynecologic cancers, accounting for 100,000 deaths in the last 10 years. The 5 year survival rates range from 6 to 51 per cent. These disappointing statistics are in part due to the late stage at which many ovarian cancers are usually discovered.

The importance of lymph node metastases from ovarian neoplasms has been virtually ignored except in the case of dysgerminoma. Little is known about the incidence of lymph node metastases in patients with epithelial cancers of the ovary and little attention is paid to this factor when planning treatment. Bilateral pedal lymphangiography, by demonstrating lymph node metastases, may prove of value in the more thorough assessment of the extent of disease—a prerequisite for intelligent management of any patient with cancer.

The present study is a retrospective analysis of 66 patients with ovarian cancer, who were examined by lymphangiography during treatment or observation at the University of Texas M. D. Anderson Hospital and Tumor Institute. Since the lymphangiograms were obtained because of some specific physical or operative finding or for the investigation of a particular problem such as ascites, the study provides no meaningful data as to the incidence of lymph node metastases in patients with ovarian cancer. Nevertheless, the frequency and distribution of metastases to lymph nodes in these patients should provide some insight into the importance of this mode of spread.

MATERIAL AND METHOD

Seventy-two lymphangiograms were performed on 66 patients with various types of malignant ovarian neoplasms. Patients were selected for lymphangiography by clinicians on a non-random basis. In the majority of cases, the presence of metastases had been established by prior biopsy or by a strong clinical suspicion because of palpatory findings. In these cases lymphangiography was performed to confirm the presence of metastases, to determine their extent, and to have a visible means of evaluating therapeutic response. Lymphangiograms were also done to determine whether nodal metastases were responsible for the production of ascites.

Histologic sections of the primary tumor in each case were reviewed and categorized according to a classification which differs slightly from that established by the Cancer Committee of the International Federation of Gynecology and Obstetrics. Clinical staging at the time of the lymphangiogram was determined utilizing the classification in Table 1.

Other data recorded included: (1) clinical staging of each patient at the time of lymphangiography; (2) presence or absence of ascites at the time of lymphangiography; and (3) surgical or clinical confirmation of the positive lymphangiogram.

TECHNIQUE

A technically adequate pedal lymphangiogram consists of opacification of lymphatics and nodes of the inguinal, pelvic, and lumbar regions to the thoracic duct. In view of the location of the first echelon lymph nodes in the lumbar area, it is essential to opacify these lymphatics to

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their junction with the thoracic duct. This can be accomplished usually by the use of 6 to 8 cc. of contrast material injected into a lymphatic in each lower extremity of an adult female. When this is inadequate to visualize the lumbar or para-aortic lymphatics, roentgenograms of the pelvis and abdomen are made. The patient is then asked to ambulate for 15 to 30 minutes and the roentgenograms are repeated to take advantage of the contrast material in the lower extremities which will move to fill lumbar lymphatics and the thoracic duct. Multiple projections are necessary to separate these structures. Magnification techniques and tomography are employed at times to enhance the presentation of this information.

LYMPHATIC DRAINAGE FROM THE OVARY (Fig. 1)

The parenchyma of the ovary contains a rich capillary network of lymphatics, chiefly in the theca externa of the follicles and corpora lutea. Lymphatics are absent in the tunica albuginea. Six to 8 large lymphatic collecting trunks emerge from the hilum, converging in the mesovarium with the efferent lymph vessels from the uterine fundus and fallopian tube to form the subovarian plexus. In the ovarian suspensory ligament, the lymphatics, with the ovarian blood vessels, cross the ureter and external iliac vessels and travel upward along the lateral aspect of the ureter to the level of the inferior pole of the kidney. Here the lymphatics turn medially, leaving the ovarian blood vessels, and cross the ureter again to reach its medial aspect. This crossing occurs at a higher point on the left than on the right. On the right, the collecting trunks diverge and drain into the precaval and lateral caval lymph nodes which lie along the inferior vena cava from its bifurcation to the renal pedicle. On the left, these lymph trunks diverge to a lesser extent and at a higher level than on the right and end in the latero-aortic and preaortic lymph nodes which are placed one above another below the left renal pedicle.

In 3 of 14 cases, Marcille discovered an accessory lymphatic pedicle from the ovary. The ovarian collecting trunks traveled in the broad ligament from the hilar plexus and then passed posteriorly under

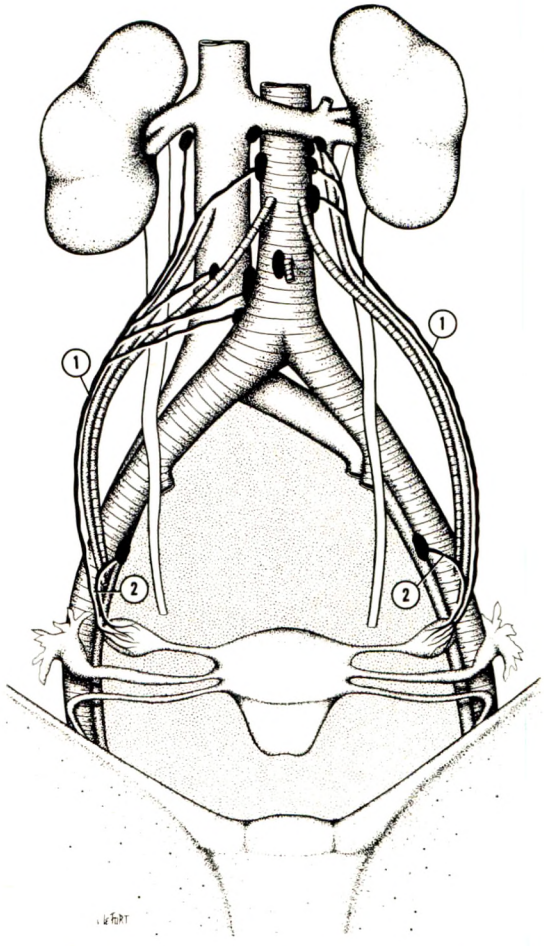

Fig. 1. Lymphatics of the ovary. Normal ovarian lymphatic drainage. 1. Para-aortic lymphatic pedicle. 2. External iliac lymphatic pedicle.

Table I

STAGE-GROUPING FOR PRIMARY CARCINOMA OF THE OVARY

Stage I.	Growth limited to the ovaries
Stage II.	Growth involving one or both ovaries with pelvic extension
Stage III.	Growth involving one or both ovaries with widespread intraperitoneal metastases
Stage IV.	Growth involving one or both ovaries with distant metastases

the peritoneum to end in a lymph node of the middle chain of the external iliac group. Anastomoses also occur between the ovarian lymph vessels and those of the uterus and the fallopian tubes, so that other variations may exist. In addition, the presence of a malignant neoplasm extending beyond the ovary with invasion of adjacent pelvic viscera and peritoneum may allow direct lymphatic continuity with the inguinal lymph nodes and with the external and common iliac lymph nodes.[14,15]

LYMPHANGIOGRAPHIC CRITERIA

Each lymphangiogram was considered either positive or negative for nodal metastases, as equivocal interpretations are of little value in the management of the patient. The criteria for diagnosis of nodal metastases are sufficiently important to merit review. The single most reliable criterion for the lymphangiographic diagnosis of metastatic neoplasm in a lymph node is a defect in the node not traversed by lymphatics (Fig. 2, *A* and *B*). Such defects are caused by tumor emboli which obstruct the marginal sinus and with subsequent growth destroy nodal tissue. The area of replacement is usually at the periphery of the lymph node, and the remaining functioning portion of the lymph node is frequently crescent-shaped. The lymphatics leading to the defect are disrupted as the result of the destructive process. Therefore, it is essential that both the lymphatic and nodal phases be technically adequate and carefully scrutinized. The appearance described can be simulated by abscess, caseous necrosis, and rarely fibrosis. In the presence of a primary malignancy, metastasis is the most likely diagnosis. On occasion the lymphangio-

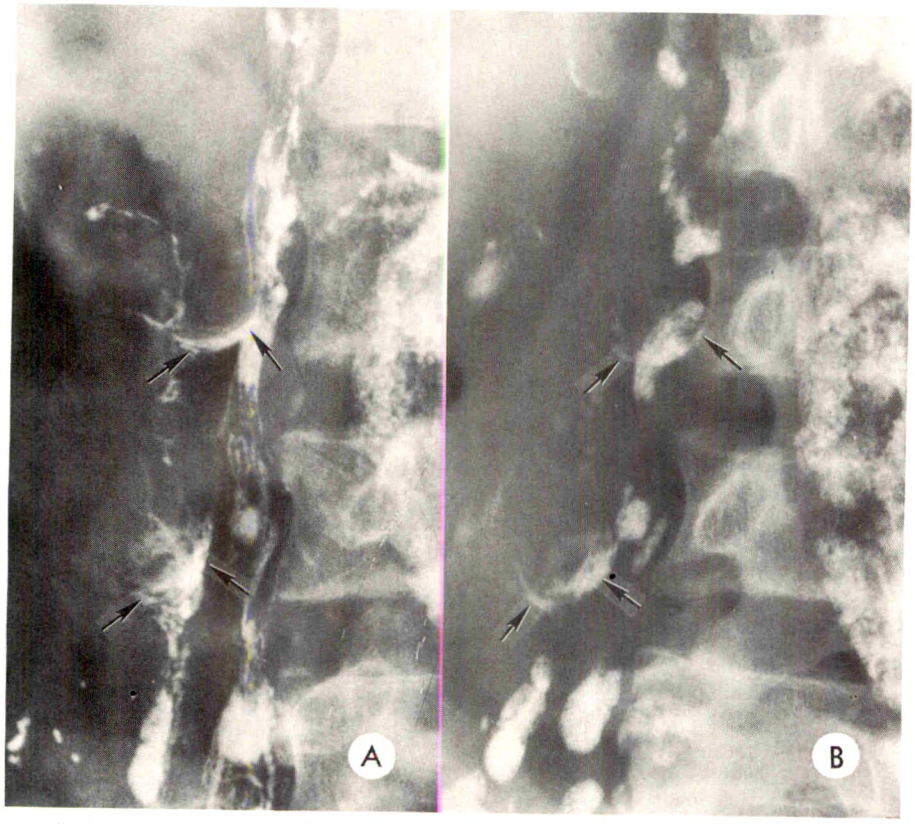

FIG. 2. Metastatic dysgerminoma from the right ovary. (*A*) The lymphatics do not traverse the filling defects in the lymph node in the lymphatic phase and (*B*) crescent defects are well shown on the nodal phase.

graphic pattern seen in a lymph node involved by metastatic dysgerminoma may be similar to that of a lymphoma (Fig. 3). The distortion of the intrinsic nodal architecture is the predominant feature.

If a lymph node is totally replaced by neoplasm, it may not be opacified; however, there may be obstruction or distortion of the lymphatics. When lymphatic channels are obstructed, there may be visualization of collateral pathways; *i.e.*, lymphatic to lymphatic, lymphatic to prelymphatic, and lymphatic to venous. Interruption of lymphatics may also be caused by prior surgery, fibrosis, or rarely infection, but in a patient with a known primary malignancy, metastatic disease is the most likely etiology.

Secondary findings of lesser specificity include a decrease in the number of opacified lymphatics and lymph nodes, stasis of contrast medium in the lymphatics, and extravasation. In the presence of these secondary findings or a totally replaced lymph node, other methods such as intravenous pyelography or venography must be employed to confirm the presence of a mass.[16]

Utilizing these criteria in patients with carcinoma of the cervix, testicle, or bladder a positive lymphangiographic diagnosis of nodal metastasis has a correlation of 90 to 95 per cent with surgical biopsies. Of those patients with nodal metastases confirmed by laparotomy, 75 to 80 per cent were diagnosed by lymphangiography. False negative examinations are due to metastases too small to detect (less than 3–5 mm.) or failure of opacification of the involved lymph nodes.[17]

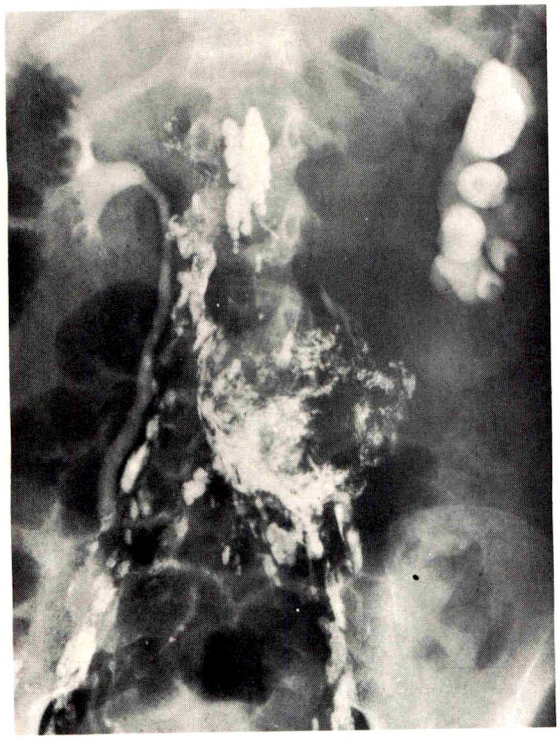

Fig. 3. Dysgerminoma of the left ovary, metastasis to left common iliac and para-aortic area. The pattern simulates lymphoma (lymphoma pattern). There is obstructive uropathy with lateral displacement of the left kidney and moderate hydronephrosis.

RESULTS

Seventy-two lymphangiograms were performed on 66 patients with 6 patients examined twice. Thirty-three (46 per cent) of these 72 lymphangiograms revealed lymph node metastases, which are presented in Table II according to the histologic classification utilized at M. D. Anderson Hospital.

Of the 33 positive examinations, the distribution of lymph node metastases was para-aortic 23 (70 per cent), iliac 19 (58 per cent), inguinal 9 (27 per cent), and supraclavicular 2 (6 per cent). Para-aortic nodal involvement alone was seen in 14 and iliac lymph node metastasis alone was demonstrated in 4. The combination of iliac and para-aortic nodal metastases was diagnosed by lymphangiography in 9 (Fig. 4, *A* and *B*). In each of the 9 patients with inguinal lymph node metastases, there was concomitant iliac lymph node involvement. Three of these patients also had para-aortic lymph node metastases. The 2 patients with supraclavicular lymph node metastases also had iliac and para-aortic nodal metastases. One of these 2 had inguinal lymph node involvement.

The relationship between lymph node

TABLE II

SUMMARY OF CASES

Histologic Classification	Lymphangiogram		Confirmation of Positive Finding		
	Positive	Negative	Surgical	Clinical	None
I. Malignant Neoplasm, NOS*	0	3			
II. Carcinoma, NOS	4	2	4		
III. Mullerian Derivative Carcinomas					
A. Serous	14	21	10	4	
B. Mucinous	1	1		1	
C. Endometroid	3	4	3		
IV. Germ Cell Tumors					
A. Dysgerminoma	8	3	5	1	2†
B. Embryonal carcinoma	0	2			
C. Teratoma, malignant	0	1			
D. Mixed germ cell tumor	2	0	2		
V. Sex Cord Tumors					
A. Granulosa—theca cell	0	0			
B. Sertoli-Leydig	1	2	1		
Total	33	39	25	6	2

* NOS= not otherwise specified.
† In 2 cases, no laparotomy was performed.

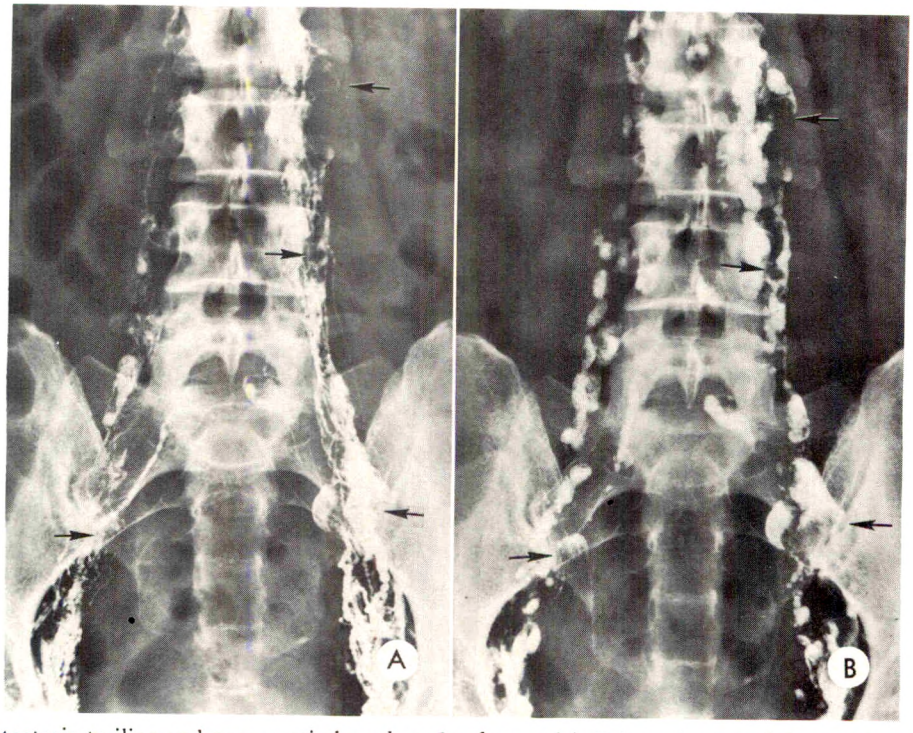

FIG. 4. Metastasis to iliac and para-aortic lymph nodes from epithelial carcinoma of the ovaries. (*A*) Lymphatic phase. The lymphatics do not traverse filling defects in the iliac and para-aortic lymph nodes. (*B*) Nodal phase.

Table III

OVARIAN CANCER AND LYMPHANGIOGRAPHY

	Distribution of Lymph Node Metastases						
	P	I	PI	IIn	PIIn	PIS	PIInS
Epithelial	6	3	3	6	2	1	1
Germ Cell	7	1	2				
Sex Cord Tumor	1						

P = para-aortic; I = iliac; In = inguinal; S = supraclavicular.

metastases and histologic classification is shown in Table III. Of the 10 patients with nodal metastases from cancers of germ cell origin, para-aortic nodal involvement was found in 9, and iliac metastases in 3. Lymph node metastases from ovarian epithelial cancers (Mullerian derivatives and carcinomas not otherwise specified), were found in 22 lymphangiograms, the para-aortic lymph nodes were involved in 13, and the iliac nodes in 16. Of these, para-aortic nodal involvement alone was seen in 6 and combined iliac and para-aortic in 7.

Clinical staging was determined by abdominal exploration. Lymphangiography was usually performed following this staging procedure. The distribution of the stages in the 66 patients was Stage I, 5; II, 9; III, 35; and IV, 17.

Seven patients with ovarian carcinoma and ascites were studied by lymphangiography to determine whether there was a relationship between lymph node metastases and ascites. Only 1 of these 7 patients had lymph node metastases. Peritoneal implants were found in all 7 patients with ascites. In 1 of these patients, the liver was small with extensive fatty infiltration. Conversely, of the 33 with lymph node metastases only 1 had ascites. The histologic classification of these 7 patients with ovarian carcinoma and ascites was epithelial neoplasms in 6 and germ cell tumor in 1, a malignant teratoma.

DISCUSSION

The distribution of lymph node metastases from a primary site is determined by the normal as well as the variations of normal lymphatic drainage. Once there is extension beyond the primary site to involve adjacent areas, subsequent metastases utilize the pathways usually draining these structures. In the event of obstruction of these channels, the distribution of lymph node metastases will depend on those collateral pathways that are present and patent, which include lymphatic to lymphatic, lymphatic to prelymphatic, and lymphatic to venous channels.

Lymph node metastases from cancer of the ovary have been demonstrated by lymphangiography.[2,3,7,9–13] Douglas *et al.*[4] found para-aortic nodal metastases in 8 (18 per cent) of 44 patients with ovarian cancer. The high incidence (46 per cent) of positive lymphangiograms in our series certainly does not reflect the true frequency of nodal metastases in cancer of the ovary. It does, however, emphasize that nodal metastases do occur in both epithelial and germ cell neoplasms of the ovary more frequently than is commonly recognized.

Lymphatic drainage from the ovary is primarily to the para-aortic lymph nodes. This distribution was confirmed by the 70 per cent incidence of para-aortic lymph node metastases in the 33 lymphangiograms with evidence of nodal metastases. However, iliac lymph node metastases were found in 58 per cent and inguinal node involvement was seen in 27 per cent. This is somewhat higher than might be expected based on Marcille's investigation revealing approximately 20 per cent of 14 cases with

an accessory lymphatic pedicle from the ovary which drained to the external iliac lymph nodes. Inguinal lymph node metastases were almost always associated with iliac nodal disease. This could be due to direct drainage to the inguinal area, as might be expected if the uterus or fallopian tubes were invaded, or due to obstruction of iliac lymphatics with retrograde spread.

The distribution of lymph node metastases was further related to the histologic types of ovarian neoplasm. The germ cell tumors almost invariably metastasized to the para-aortic lymph nodes (90 per cent) and to a lesser extent to the iliac lymph nodes (30 per cent). On the other hand, the ovarian cancers of epithelial cell origin metastasized to the iliac lymph nodes in 73 per cent, to the para-aortic lymph nodes in 60 per cent, and to the inguinal lymph nodes in 41 per cent. This suggests that the neoplasms of germ cell origin are usually confined to the ovary and spread along the anatomically defined lymphatic drainage. Epithelial cell malignancies are more likely to extend through the capsule to involve adjacent pelvic viscera, which may account for the frequency of pelvic nodal metastases, both to inguinal and iliac lymph nodes. In many instances the ovarian lesion was huge and was described as adhering to the pelvic walls. The iliac lymph nodes may be involved by contiguity. The demonstration of para-aortic in addition to iliac and inguinal nodal metastases in some of these cases may be spread by continuity.

Mediastinal and supraclavicular nodal metastases are most probably a manifestation of variations in normal lymphatic distribution of the thoracic duct. This would explain the apparent continuity of metastases in the pelvic, para-aortic, and supraclavicular lymph nodes in 2 cases in this series.

Hanks and Bagshaw[6] describe the use of lymphangiography as an aid in staging and planning therapy. Para-aortic lymph node metastases were demonstrated in 7 of 20 patients, even though these areas were palpably normal at surgical exploration. As the result of the lymphangiographic findings, the stage was changed in 6 of these patients and the therapy altered.

Ascites, although a frequent finding in patients with ovarian cancer, was found in only 7 patients in this series. This may have been a product of the nonrandomized selection. The mechanisms underlying the development of ascites in patients with peritoneal carcinomatosis are still obscure. Ascites may be the result of either an increased inflow or obstruction to outflow of fluid from the peritoneal cavity. Lymphangiography was performed in these patients to determine if there was a relationship between lymph node metastases producing lymphatic obstruction, lymphatic fistulae, and ascites. Only 1 of 33 with lymph node metastases had ascites. On the other hand, each of the 7 patients with ascites was found to have peritoneal implants of ovarian cancer. Increased production of fluid has been attributed to an increased capillary permeability to protein, especially at the peritoneal tumor implants.[8] Perhaps peritoneal implants encroach upon the available surface for fluid absorption by interfering with the lymphatic network draining the peritoneal cavity. Tumor cells were found obstructing diaphragmatic lymphatics in experimentally produced ascites due to peritoneal carcinomatosis.[5] Another etiologic agent to be considered in the presence of ascites in patients with ovarian cancer treated by total abdominal irradiation is radiation hepatitis.[18]

SUMMARY

Lymphangiography can be of assistance in pre-treatment staging and thereby influence management of patients with ovarian cancer.

The distribution of lymph node metastases was related to the histologic type of ovarian neoplasm. Tumors of germ cell origin more frequently spread to para-aortic lymph nodes, while epithelial neoplasms of the ovary metastasized to the

pelvic and para-aortic lymph nodes, apparently in continuity.

In this series, lymph node metastasis from ovarian cancer was seldom associated with ascites.

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PREOPERATIVE IRRADIATION IN RENAL CANCER*

EVALUATION OF RADIATION TREATMENT PLANS

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THE survival figures for radical nephrectomy indicate an over-all survival rate of 38 per cent at 5 years and 27 per cent at 10 years.[9] Once there is extension to the renal vein or pericapsular invasion, the 5 year results drop from 63 per cent (for encapsulated tumors) to 31 per cent and 25 per cent, respectively. Furthermore, the types of nephrectomy vary from one institution to another, and postoperative irradiation has been employed without careful definition of its indications. It is assumed that irradiation would be employed in cases of more extensive disease, following the rules of natural selection utilized in nonrandomized clinical studies. From the tabulation of survival figures of such reports[1,2,6,12–14,16,20] radiation therapy has been shown to improve results when employed postoperatively (Table 1). A stimulus for combining irradiation and surgery can be traced to the report of Riches *et al.*[16] They noted that the 5 year survival improved from 20 per cent to 49 per cent for nephrectomy and postoperative irradiation in a series of 1,746 cases gathered from 26 centers in the British Urological Association. Other investigators such as Charteris,[2] Bratherton,[1] and Ochsner[13] have shown a similar gain in survival at 5 years of 10 per cent to 30 per cent, but none of their studies meet the criterion of being prospective, controlled studies; therefore, they remain inconclusive.

A combination of radiation therapy and surgery may be more effective than nephrectomy alone in the treatment of primary renal cancers. The high conversion percentage of localized cancers to disseminated metastases demands a general

TABLE I

REVIEW OF LITERATURE

Source	Survival (Years)	Nephrectomy (Per Cent)	Nephrectomy+ Irradiation
Flocks and Kadesky[6]	5	48	52
	10	23	33
Riches *et al.*[16]	5	30	49
	10	17	27
Charteris[2]	5	26	36
Bratherton[1]	5	29	43
	10	26	33
Ochsner[13]	5	9	39
Murphy and Mostofi[12]	mean	3.1 years	5.4 years
		2.1 years	2.3 years
Peeling *et al.*[14]	5	52	25
Skinner *et al.*[20]	5	57	50

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treatment stratagem that will also affect this aspect of the problem. The effectiveness of radical nephrectomy in controlling local disease, even when extensive, suggests that local or regional recurrence may not be of importance in reducing metastases. However, the literature deals mainly with survival figures and there are few data as to local control following different treatment modalities.

It has been suggested that there may be an improvement in survival with the use of preoperative irradiation, based particularly upon the work of Flocks and Kadesky.[6] They found that the gain in survival was 50 per cent when irradiation was given preoperatively, as compared to 33 per cent for postoperative irradiation. Further support for this observation is noted in Riches' experience[15,16] in the 11 cases which were originally considered inoperable, but were converted to operable status by preoperative irradiation. In 16 cases, 5 long-term survivors were recorded, in whom there were high grade tumors and renal vein invasion. Pilot studies by Cox *et al.*[3] show this to be a feasible approach, and suggest a radiotherapeutic effect in comparison with some of the pre- and post-treatment arteriograms.

I. RATIONALE FOR CLINICAL TRIAL OF PREOPERATIVE IRRADIATION

A. THEORETIC RADIOBIOLOGIC ADVANTAGES

The advantages of preoperative irradiation are:

(1) Reduction of the viability of tumor cells released at surgical manipulation, thereby reducing metastases.
(2) Reduction of microscopic and gross pericapsular and renal spread, thereby increasing the operability and resectability of the tumor and avoiding resection through its marginal extension.
(3) Reduction of the incidence of local recurrences, lowering the likelihood for this pathway of metastases.
(4) Sterilization of microdeposits in lymph nodes and prevention of metastatic spread into the subclavian vein *via* lymphatics.

B. DEFINING THE TARGET VOLUME

The target volume is the primary renal cancer, its lymph node drainage, and venous drainage into the vena cava. "The importance of lymph node drainage has only recently been appreciated as a source for metastases since hematogenous spread has been so heavily emphasized in the literature."[18] This is understandable because the accessibility of the renal vein to surgical inspection and radiographic study has permitted documentation of its involvement. By contrast, the peri-aortic lymph nodes above the renal pedicle are not routinely visualized on pedal lymphangiography, nor are they usually inspected at the time of surgery. There is evidence to indicate that a positive lymphangiogram is expected in 20 per cent to 40 per cent of presenting cases.[7] The operative findings of positive lymph nodes are also in this range of 20 per cent to 30 per cent, depending upon the extent of the primary lesion, particularly when pericapsular invasion has occurred. The best results reported in the literature are those of Robson,[17] with a survival rate of 66.3 per cent at 10 years, compared to 22 per cent for a 10 year survival in a large collected series[8] treated by radical nephrectomy. The improvement is attributed to a thoracoabdominal approach, in which the removal of regional lymph nodes and primary occlusion of the renal vein are done before tumor manipulation along with resection of the kidney and perinephric envelope. Robson's dissection of renal lymph nodes up to the diaphragm and down to the aortic bifurcation may be an important factor; this is not usually done in radical nephrectomies.

The surgical ability to resect venous extensions of renal cancers aggressively and to yield long-term survival is an argument for including the renal vein and inferior vena caval segment up to the left auricle in the treatment field. The results

reported by Skinner *et al.*[20] for nephrectomy particularly with a focus on resection of renal vein thrombi, indicate a survival at 5 years of 66 per cent. This remarkable achievement is akin to survival results with nephrectomy in Stage I renal cancer and is superior to other reports.[9] When invasion of the capsule or perinephric fat occurs, survival decreases sharply. Even with inferior vena caval involvement as the only evidence of spread except for the intracapsular component, they report a 55 per cent 5 year, and a 40 per cent 10 year survival. Their use of irradiation either prior to or subsequent to surgery is too sporadic to warrant any conclusion as to its value.

C. SELECTION OF OPTIMUM DOSE-TIME FACTORS

The optimum dose-time relationship is difficult to define. The upper abdomen is one of the most challenging volumes to irradiate to higher doses due to the low and moderate dose thresholds of vital viscera and organs located in this region. The schedule chosen for the national protocol was a tumor dose of 4,500–4,800 rads in $4\frac{1}{2}$ to 6 weeks, with a variation of ± 10 per cent for other parts of the tumor. A daily dose of 200 rads and a weekly dose of 1,000 rads is preferred, but a daily rate of 150 rads times 6 for a weekly rate of 900 rads is an alternative, if the fields are large and the tolerance is poor. Kligerman[10] suggested a single dose of 800 rads, but the large fields required and the known low tolerance of normal tissues in this area would suggest a need for pilot or preliminary tests for the feasibility of this idea. The rationale is to obtain rapid tumor destruction efficiently, followed by immediate surgery, as the best strategy to reduce hematogenous spread. A dose level of 3,000 rads was employed in fractional daily increments by Richies.[15] The use of total doses greater than 5,000 rads in large segments of the upper abdominal area increases the risk of delayed complications; although it affords a chance for better tumor control, this would be offset by a predictable rise in incidence or irradiation injuries.

The chosen dose of 4,500 rads is believed to be within tissue tolerance levels and is adequate to sterilize microdeposits in lymph nodes[5,11] and peripheral extensions of tumor cords.

D. ACCURACY OF DIAGNOSIS AND STAGING

The need to have an accurate diagnostic procedure for diagnosing the tumor and defining the tumor volume is a mandatory prerequisite before preoperative irradiation can be done. The reported accuracy of renal arteriography is 90 per cent to 95 per cent fulfilling these requirements, making the use of irradiation possible without a tissue diagnosis.[4]

II. RADIATION TREATMENT PLANS FOR PREOPERATIVE IRRADIATION

It is essential to define the geographic extent of the tumor and to determine the placement of vital viscera in the treatment field. The major problems in treatment planning relate to target volume (Fig. 1). The inclusion of large renal masses, the retroperitoneal nodal drainage, renal vein and inferior vena cava in treatment portals encompasses such structures as the liver, small bowel, stomach and spinal cord.

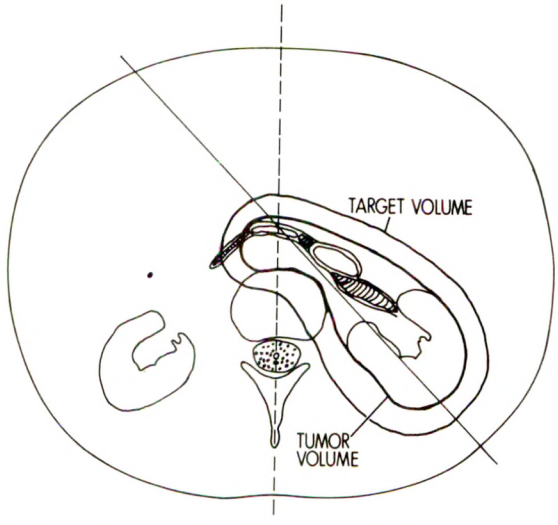

FIG. 1. Cross section outline of kidney region with the outline of a standardized target volume.

Despite efforts to bias, angle, wedge or position fields in order to concentrate the dose on one area, the opposite kidney presents a shielding problem. It is not surprising that there are numerous instances when only an opposed field arrangement is feasible, due to the large target volume. Let us consider the different variations possible and some of their theoretic advantages and disadvantages.

Although the tumor dose ideally should be uniform throughout the tumor volume, it is difficult to achieve; and in practice, the isodose surface encompassing the entire mass is designated as the tumor dose. In some arrangements, this is not possible and the dose through the center of the tumor is utilized. A variation of ±500 rads in the tumor volume is approximately ±10 per cent from maximal to minimal dose. A preferable variation would be ±225 rads, or ±5 per cent. This uniformity in tumor dose needs to be accomplished while remaining within tolerance doses of surrounding normal tissue,[19] *i.e.*, the spinal cord should receive no more than the tumor dose of 4,500 rads. Increased risks occur in treating biased fields and when the nodal drainage is to be included. The liver dose becomes critical if large volume irradiation is delivered on the right side. Levels beyond 3,500 rads may exceed tolerance and lead to central vein thrombosis. The stomach and small intestine will react and cause functional changes before the 4,500 rad level, but severe damage should be avoided with this prescribed schedule. Doses exceeding 5,000 rads may produce severe bowel injury. The pancreas and biliary tree are quite radioresistant, but the opposite kidney should be safeguarded against excessive exposure. Doses of 2,000 rads or less can be tolerated, but since this is the only remaining kidney it is important to keep the dose as low as possible. A series of possible treatment plans is illustrated indicating the difficulties in fulfilling the criteria of the protocol. The tumor volume is stippled, the isodose curves are shown in percentages of the surface dose, and the tumor dose is normalized to the 4,500 rad level.

Plan A: Single Posterior Field Obliqued 15°–30° (Figure 2, *A–D*)

This schema is useful for postoperative irradiation of renal cancer residuum in the fossa, but unless the lesion is of small size this arrangement leads to a large variation in tumor dose. The nodal drainage receives 3,200 rads for 4,500 rads to the tumor. Its main advantage is lowering the dose to the liver to acceptable levels. If the field is not angled, a large volume of the liver is included when a right-sided mass is treated. The angle of obliquity avoids a high dose to the spinal cord and the opposite kidney.

Plan B: Opposed Fields (Unweighted) (Figure 2, *A–D*)

This arrangement is used when large tumor volumes are to be treated. It is simple and allows for incorporation of lymph nodes and major veins. The disadvantage lies in delivering tumor midplane doses of 4,500 rads to the thick patient (>25 cm. width) when doses to the spinal cord and liver can exceed tolerance.

Plan C: Biased Fields 3:1 or 2:1, Obliqued (Figure 2, *A–D*)

The major advantage of the 3:1 biased field is a compromise between the uniform dose of equally weighted fields and the extreme variations in tumor dose of a single field. Such a ratio of 3:1 is again restrictive to smaller tumor volumes. The obliquity to field direction lowers the liver volume on the right side, avoiding the spinal cord and the opposite kidney.

A 2:1 arrangement is perhaps the best compromise between uniformity in tumor dose and sparing of normal tissue such as liver and stomach in the anterior part of the upper abdomen. Note that the nodal dose is higher but not in the 4,500 rad range. The spinal cord and opposite kidney doses are low and acceptable. The bowel receives no more than 4,500 rads, which is within tolerance levels.

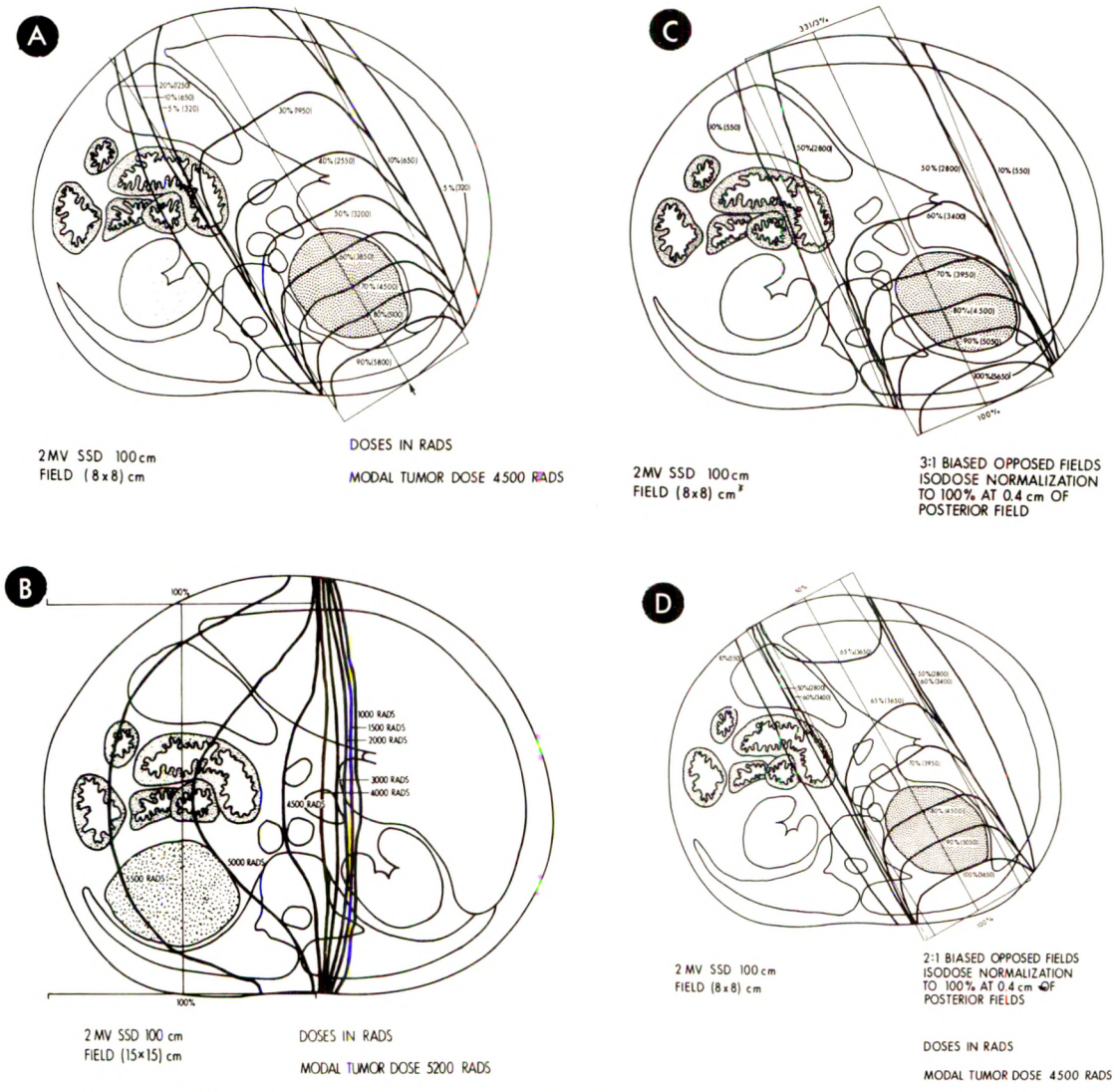

FIG. 2. (*A–D*) These arrangements are parallel-opposed fields with obliquing and biasing.

PLAN D: OSCILLATION 220°
(Figure 3, *A–D*)

This plan provides an excellent distribution of dose (4,500 rads) throughout the tumor volume; the dose to the nodal region is likewise acceptable (3,500 rads ±500). Low doses are delivered to the spinal cord (2,000 rads ±250), but higher doses are delivered to the opposite kidney and to the liver. The dose of 1,100 rads to the opposite kidney is of concern, but this is believed to be within tolerance levels in the adult. As tumor volume increases, the therapist's ability to spare normal tissues is less. The liver dose of 2,300 rads is also in a range where adverse effects may result, but is below tolerance levels recorded.

PLAN E: TWO WEDGED 45° FIELDS
(Figure 3, *A–D*)

The advantages of wedged fields relate to uniformity of dose distribution in small tumor volume, while avoiding excessive doses to the spinal cord and opposite kidney. The dose to the liver and bowel is also reduced. The nodal dose falls rapidly due to edge effects of beams.

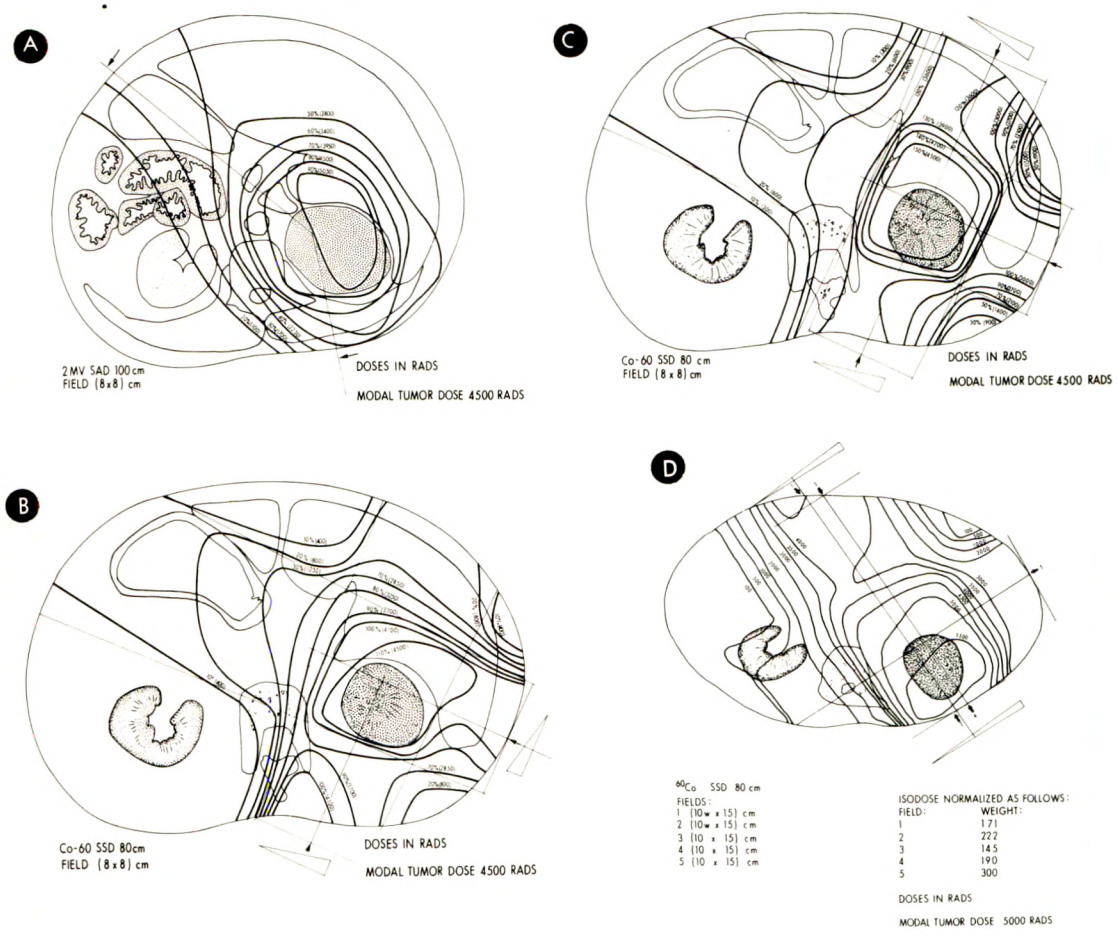

FIG. 3. (*A–D*) These arrangements are wedge fields and arc therapy.

PLAN F: THREE FIELDS, TWO WITH 45° WEDGES
(Figure 3, *A–D*)

This unusual arrangement is a pair of opposed wedged fields obliqued toward the side of involvement. A third field on the ipsilateral side laterally biases the tumor dose volume, while lowering doses to the bowel. The nodal drainage is inadequately treated and is in a rapidly falling zone between 900 and 3,600 rads. The dose to the large volume of the liver is high, *i.e.*, 3,500–4,500 rads, and would be of concern.

PLAN G: FIVE FIELD CROSSFIRE WITH TWO WEDGED FIELDS AND BOOSTER FIELD
(Figure 3, *A–D*)

This is a modification of the previous 3 field arrangement. The major purpose of the 2 smaller oblique fields is the reduction of the spinal cord dose, while increasing the dose to the nodal drainage. These are essentially booster fields. It appears more complicated on paper than it actually is in clinical execution when the fields are being treated.

III. DISCUSSION

1. EVALUATION OF RADIATION TREATMENT PLANS

Of the first approximately 155 patients randomized to radiation therapy treatment included in the national protocol, there are 101 for whom detailed evaluation of preoperative irradiation techniques is possible. The dose to the primary renal cancer was considered adequate in 90 per cent, or 89 of the cases. The target volume dose ranged from 4,150–4,770 rads in most cases, but the minimal to maximal dose

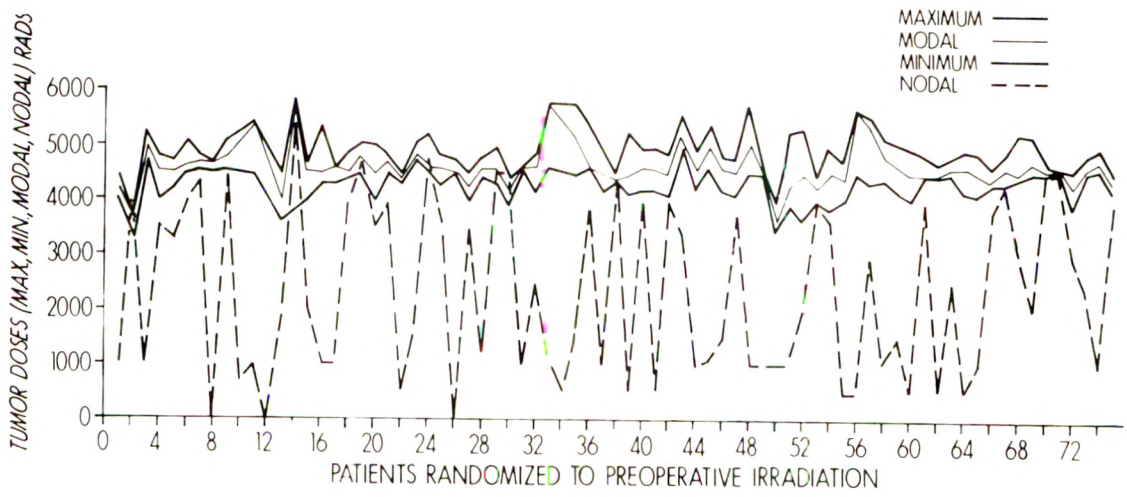

FIG. 4. Sequential plotting of the maximal, modal, minimal, and lymph node doses indicates a variation of ± 10 per cent in filling the dose prescriptions. The nodal dose is even at greater variance with more than ⅔ of the cases not receiving the full doses prescribed in the protocol.

ranged from 2,800–6,000 rads. These maximal and minimal dose levels for these first 73 patients were even more at variance than was initially anticipated (Fig. 4).

The inclusion of regional or first station lymph nodes in treatment fields varied considerably: in 21 cases the lymph nodes were considered to have been adequately treated (>4,000 rads), in 19 instances the lymph nodes were underdosed (3,000–4,000 rads), and in 52 cases, inadequately treated (>3,000 rads). The renal vein and vena caval doses are similar to those mentioned for regional lymph nodes. Therefore, the resection of primary cancer and kidney should also include dissection of lymph node drainage and, if present, the venous tumor thrombus. Irradiation of the involved lymph node presents tolerance problems in achieving full and adequate doses. By the analysis of the radiation data in this study, the surgical removal of lymph nodes is to be reinforced, since in about 50 per cent of treatment plans, doses were inadequate for treating occult disease and the irradiation of the positive lymph nodes would require doses exceeding tolerance for many vital viscera in this area, *i.e.*, 5,000 to 6,000 rads.

The most commonly used treatment plans were the biased field arrangement, either 3:1 or 2:1, and simply opposed fields with no angling or weighting. The use of simple field arrangements was due to the large tumor volumes being treated.

Doses to critical structures were within tolerance levels. Spinal cord doses were usually less than 3,000 rads, but in a few instances levels of 5,000, 5,400, and 4,700 rads were found. Doses to the stomach were occasionally high, *i.e.*, 4,000–5,000 rads. The opposite kidney rarely received doses greater than 500 rads. One arrangement with biased anterior fields, 2:1 was discontinued due to the excessive doses being delivered to the liver. To date, no severe or late radiation complications have been noted.

2. RESULTS OF PREOPERATIVE RADIATION THERAPY IN RENAL CANCER

Prior to this national cooperative study, the Rotterdam radiotherapists and urologists launched a clinical trial of preoperative irradiation in 1965 in which 3,000 rads was the selected tumor dose. The report by Van der Werf-Messing[14,21] shows no advantage for the preoperatively irradiated group at this dose level and does not support the initial impression of a small gain in survival. Most impressive was the dif-

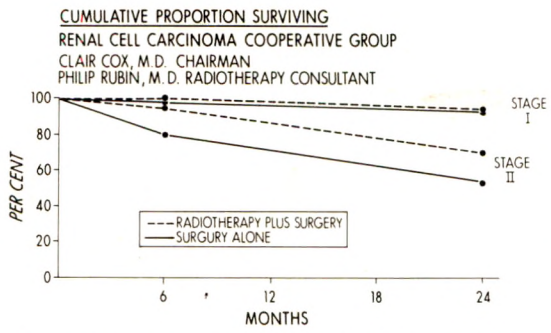

FIG. 5. Graphic display of survival figures for Stage II lesions indicates a gain in survival in preoperative irradiation of 10 to 15 per cent at 1 and 2 years.

ference in resection rates of P2 (pericapsular extensions) and P3 (venous and lymphatic invasion) cancers. There was only a 20 per cent *versus* 33 per cent incomplete operability rate for P2 tumors and a 22 per cent *versus* 52 per cent inoperability rate for P3 tumors, suggesting that prior irradiation allowed for more complete resections.

As in the Rotterdam study, there is a better survival, *i.e.*, 15 per cent to 20 per cent, after 2 years for preoperative irradiation and nephrectomy (Fig. 5). The number of patients available for analysis is too small to be conclusive or significant statistically. The time to development of metastases was delayed if the tumor was completely resected, which occurred more often in the preoperative irradiated group.[21] Patients with residual tumors have a poorer prognosis than those with complete removal.

SUMMARY

1. Analysis of radiation treatment plans of a preoperative irradiation study of the kidney indicates that the primary cancer has been treated to levels of 4,500 rads ± 10 per cent in 90 per cent of the instances.

2. The major problem, from the point of view of the radiation therapist's treatment planning, is the delivery of adequate doses to the regional nodal volume. Only 25 per cent received the prescribed dose. Special booster fields are required.

3. Surgical resection of regional lymph nodes and renal vein thrombus, if present, is recommended, since the deliverance of full radiation doses is not likely without exceeding tolerance of vital normal tissues.

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SURGERY AND POSTOPERATIVE RADIOTHERAPY IN THE TREATMENT OF SOFT TISSUE SARCOMAS IN ADULTS*

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UNTIL recently, most reports in the literature have concluded that surgery is the only effective treatment for soft tissue sarcomas. Radical surgery is advocated, since experience has shown that the local recurrence rate after simple excision is greater than 80 per cent.[1,6] Most lesions of the extremities are managed by a soft-part resection or by ablation, *i.e.*, amputation, disarticulation, and fore- or hind-quarter resections. In spite of the radical surgery, the local recurrence rate reported in 2 large series is 28 and 29 per cent.[2,5]

Recently, there have been reports in the literature citing encouraging results obtained by treatment with radiation therapy alone or radiation therapy combined with surgery.[7,10] This report presents the results of our experience in a selected group of patients treated by conservative surgical excision and postoperative radiation therapy.

CASE MATERIAL

The charts of all patients with soft tissue sarcomas treated with megavoltage radiation therapy from 1954 through 1971 were reviewed. Only those patients meeting the following criteria were included in the study: (1) 16 years of age or older; (2) no evidence of distant metastasis on admission; (3) gross tumor removed by a conservative surgical excision; and (4) postoperative radiation therapy of at least 5,000 rads tumor dose in 5 weeks. Patients with tumors arising in organ sites, *e.g.*, the uterus, were excluded.

TABLE I

SOFT TISSUE SARCOMA

(1954 through 1971)

Malignant fibrohistiocytoma	10
Liposarcoma	12
Fibrosarcoma	9
Rhabdomyosarcoma	14
Leiomyosarcoma	4
Neurofibrosarcoma	24
Synovial sarcoma	13
Angiosarcoma	2
Epithelioid sarcoma	2
Unclassified sarcoma	10
Total	100

The histopathologic diagnosis of the 100 patients fulfilling the above criteria is presented in Table 1. During the 18 year period covered by the study, the histopathologic material was reviewed a number of times, and numerous diagnoses were changed. The data are presented according to the current diagnosis rather than the diagnosis made at the time of treatment.

The majority of the patients (64/100) was more than 40 years of age. The patient distribution by histopathologic type was independent of age except for rhabdomyosarcoma (9/14 patients were less than 30 years of age). There was a slight preponderance of males in all age groups: the entire group was composed of 56 males and 44 females.

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TREATMENT

Most of the patients presented at M. D. Anderson Hospital after incisional biopsy, simple excision, or with gross recurrence after surgery. Patients with gross tumor underwent a re-excision with a limited margin rather than the standard 5 to 7 cm. margin used in radical resections. Thus, in this selected group of patients, there was no clinically detectable gross disease at the start of radiotherapy. Radiation therapy was started when healing was complete, usually within 3 to 4 weeks of the surgical excision.

In July 1961, a study was started of patients who had lesions arising in the distal portion of the extremity and for whom amputation had been recommended. These patients were treated under conditions of relative hypoxia by means of the tourniquet technique.[8] Molecular oxygen is one of the most potent radiation sensitizers yet studied. The ratio of the radiosensitivities for anoxic to aerobic cell is about 2 to 2.5. In order to eliminate the differential in oxygen tension between the normal and malignant cells, a tourniquet was placed around the proximal portion of the extremity for 30 to 45 minutes prior to irradiation. A weekly tumor dose of 2,000 rads was delivered in 2 fractions of 1,000 rads on 2 consecutive days for a total of 14,000 rads in 43 days. The reduced oxygen tension allowed a two-fold increase in tumor dose, while achieving the same acute skin reactions as with conventional radiotherapy (7,000 rads in 7 weeks). Once the efficacy of the tourniquet technique was established, patients were randomized to either the tourniquet technique or conventional radiotherapy.

Twenty-five patients were treated with the tourniquet technique, and the remaining 75 were irradiated with a megavoltage external beam, usually Co^{60}, using conventional fractionations, *i.e.*, 1,000 rads tumor dose per week in 5 fractions. The total tumor dose varied from 6,500 rads in $6\frac{1}{2}$ weeks to 7,500 rads in $7\frac{1}{2}$ weeks, employing a shrinking field technique after 5,000 rads tumor dose. Most patients, however, received 7,000 rads tumor dose in 7 weeks.

Chemotherapy was used in selected patients in the latter portion of the study period. Four of the 14 patients with rhabdomyosarcoma received concomitant chemotherapy (vincristine and cytoxan) at the time of the irradiation of the primary tumor.

RESULTS OF TREATMENT

Table II shows the distribution by anatomic site and the status at 2 years of the 100 patients. Sixty-eight patients are living free of disease; however, 5 of the 68 patients had a recurrence at the primary site and were salvaged by subsequent surgery. Fifteen patients died with recurrent tumor at the primary site; 9 of these 15 patients also had distant metastases. Thirteen patients died within 2 years of distant metastasis which was the only manifestation of their disease.

Fifty-three of the 100 patients have been followed 5 years, and their status at 5 years is shown in Table III. Thirty-one of the 53 patients (58.5 per cent) are living free of disease. Ten patients died with recurrent disease at the primary site; 5 of the 10 patients also had distant metastasis. Nine patients died with distant metastasis alone.

LOCAL RECURRENCE

The recurrence time distribution for failure to control the primary lesion is shown in Figure 1. A minimum follow-up of 24 months is adequate to judge the effectiveness of the treatment, since 80 per cent (20/25) of the local recurrences occurred within 2 years. All recurrences were manifest by 36 months.

The incidence of local recurrence, according to the histopathologic type and the location of the primary tumor, is shown in Table IV. Although the frequency in primary failure varies with the anatomic site (7.7 to 45 per cent), it appears to be independent of the histology with the exception

TABLE II

SOFT TISSUE SARCOMA

(1954 through 1971)

STATUS AT 2 YEARS

Site	Total Cases	NED	Cause of Death			
			P+DM	N+DM	DM	UNK
Head and neck	11	7 (1)*	4			
Trunk	27	16	8	1	2	
Upper extremity	26	21 (1)		1	4	
Lower extremity	36	24†(3)	3	1	7	1
Total	100	68 (5)	15	3	13	1

* ( ) Patients with recurrence at primary site salvaged by surgery.
† Two patients treated with tourniquet technique had an amputation for complication.
NED—Living—No Evidence of Disease.
P+DM—Primary failure+Distant Metastasis.
N—Node Failure.
DM—Distant Metastasis only.
UNK—Unknown Cause.

of rhabdomyosarcoma (8/14, 57 per cent). Rhabdomyosarcoma accounts for 4 of the 5 failures in the head and neck and 3 of the 9 failures in the trunk. Four of the 14 patients with rhabdomyosarcoma received concomitant vincristine and cytoxan (1 of the 4 had a local recurrence).

In patients with upper extremity sarcomas, the only local recurrences were in the arm (2 of 5 patients) (Table v). In patients with lower extremity sarcomas, 5 of 16 thigh lesions and 4 of 10 leg lesions recurred locally. There were no local recurrences in the knee, ankle, foot, or distal portion of the upper extremity.

FIRST MANIFESTATION OF METASTASIS

Soft tissue sarcomas have a high incidence of metastasis. Distant metastasis was the first spread of disease in 31 patients, as compared with lymph node metastasis in 3 patients. Twenty-four of the 31 patients with distant metastasis (78 per cent) developed them within 24 months

TABLE III

SOFT TISSUE SARCOMA

(1954 through 1968)

STATUS AT 5 YEARS

Site	Total Cases	NED	Cause of Death			
			P+DM	N+DM	DM	UNK
Head and neck	8	4	4			
Trunk	8	4	3		1	
Upper extremity	16	13			3	
Lower extremity	21	10†	3	1	5 (1)*	2 (1)
Total	53	31	10	1	9 (1)	2 (1)

* ( ) Patients with recurrence at primary site salvaged by surgery.
† Two patients treated with tourniquet technique had an amputation for complication.

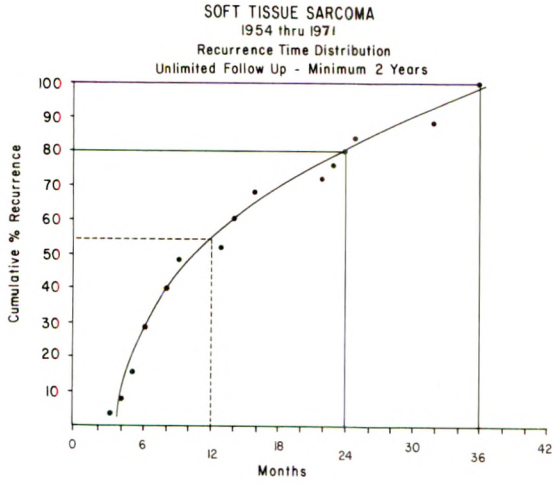

FIG. 1.

of treatment. The incidence of distant metastasis varied with the site of the primary tumor (18 to 41 per cent). Twelve of the 31 patients had uncontrolled primary tumors when the metastasis became manifest (8/12 had lower extremity primaries). Pulmonary metastasis was the initial site in 25 patients (80.6 per cent). Surgery controlled pulmonary metastases in 3 patients.

Lymph node metastasis was the first manifestation of spread in 3 patients. The primary tumor was controlled in all 3 patients. Two of the 3 patients had rhabdomyosarcoma and had received concomitant chemotherapy at the time of the irradiation of the primary tumor.

COMPLICATIONS

Most patients will exhibit some degree of clinically detectable fibrosis in the irradiated area. Significant complications in the head and neck and trunk area are virtually nonexistent (1 patient developed persistent difficulty in swallowing). Eleven of the 25 patients (44 per cent) treated with the tourniquet technique developed complications as compared with 6 of 37 patients (16 per cent) with lesions of the extremities treated by conventional techniques (Table VI). All 4 patients requiring amputation because of complications had been treated by the tourniquet technique.

DISCUSSION

The local recurrence rate in patients treated by conservative excision and postoperative radiotherapy is 25 per cent

TABLE IV

SOFT TISSUE SARCOMA
LOCAL RECURRENCE BY HISTOLOGY AND SITE
(1954 through 1971)
Unlimited Follow-up—Minimum 2 Years

Diagnosis	Head and Neck	Trunk	Upper Extremity	Lower Extremity	Total
Malignant fibrohistiocytoma		1/1	1/3	1/6	3/10
Liposarcoma		1/4	1/2	2/6	4/12
Fibrosarcoma	0/2	1/3	0/2	1/2	2/9
Rhabdomyosarcoma	4/4	3/4	0/3	1/3	8/14*
Leiomyosarcoma		1/2	0/1	0/1	1/4
Neurofibrosarcoma	0/1	2/9	0/6	4/8	6/24
Synovial sarcoma		0/1	0/6	0/6	0/13
Angiosarcoma	0/2				0/2
Epithelioid sarcoma			0/2		0/2
Unclassified sarcoma	1/2	0/3	0/1	0/4	1/10
Total	5/11	9/27†	2/26	9/36	25/100

* RMS—Highest incidence of local recurrence 57 per cent. Accounts for 4/5 failures in head and neck and 3/9 in trunk.
† Buttocks—9, retroperitoneal—9, axilla and shoulder—4, single sites—5.

(Table IV). For lesions of the extremities, the recurrence rate is 17.8 per cent (11/62). This compares favorably with the local recurrence rate of 28 per cent for lesions in the extremities treated by radical surgery. Six of the 11 local recurrences in extremities were subsequently controlled by surgery, whereas only 1 of the 14 recurrences in the head and neck and trunk were controlled. The local recurrence rate in the distal portion of the extremity is only 9.7 per cent (4/41) (Table V). A mass may grow to 10 or 15 cm. in the thigh, leg, or arm before it is detectable, whereas a 2–3 cm. mass is easily noted in the hand, foot, or around the joint. Thus, lesions arising in the latter areas are diagnosed early before they spread between the fascial planes. In spite of generous radiation fields, 3 of the 11 local recurrences in the extremities occurred outside the irradiated volume. Some recurrences were more than 5 cm. beyond the treated volume, which itself extended at least 5 cm. beyond the scar. These recurrences show that soft tissue sarcomas spread along the fascial planes for great distances.

The rationale for removing all gross tumor by a conservative surgical excision followed by radiation therapy is that the remaining subclinical disease can be destroyed with moderate doses of irradiation. This concept has been reported for carcinoma of the head and neck[4] and of the breast,[3] *i.e.*, 5,000 rads in 5 weeks sterilizes more than 90 per cent of subclinical disease. These results show that this concept is also applicable to the sarcomas which can be grossly removed by a conservative excision. Massive lesions cannot be treated by this approach, since a conservative excision is not possible.

Many patients are referred to M. D. Anderson Hospital after a simple "shelling-out" of the tumor. Each patient must be carefully evaluated regarding the adequacy of the initial procedure. Re-excision is indicated, if there is a possibility that gross tumor remains. This decision is based on the clinical examination and the information obtained from the referring physician. Occasionally, in lesions of the extremities, xerography and/or arteriography may be useful by defining deep-seated, residual areas of the tumor. If re-excision is necessary, whether for suspected or obvious gross tumor, the location and length of the scar as well as the stab wounds for drainage must be planned so that they can be easily encompassed in irradiated fields which do not include the whole circumference of the limb. It is also important for the surgeon to place clips marking the ex-

TABLE V

SOFT TISSUE SARCOMA

(1954 through 1971)

INCIDENCE OF FAILURE IN EXTREMITIES

(Unlimited Follow-up—Minimum 2 Years)

Upper Extremity		Lower Extremity	
Arm	2/5	Thigh	5/16
Elbow	0/3	Knee	0/6
Forearm	0/10	Leg	4/10
Wrist	0/2	Ankle	0/3
Hand	0/6	Foot	0/1
Total	2/26	Total	9/36

TABLE VI

SOFT TISSUE SARCOMA

(1954 through 1971)

COMPLICATIONS—EXTREMITY LESIONS

(62 Patients)

	Tourniquet* Technique	Conventional† Technique
Amputation	4	0
Soft tissue necrosis	2	2
Edema of distal extremity	1	3
Significant fibrosis	3	1
Bone necrosis	1	0
Total	11/25 (44%)	6/37 (16%)

* 14,000 rads tumor dose in 43 days, twice a week 1,000 rads.
† 7,000 rads tumor dose in 7 weeks.

tent of the gross tumor, especially in abdominal lesions.

The irradiation techniques vary with the location of the primary tumor. The surgical field must be included with a generous margin (5 to 7 cm. in extremity lesions) in the irradiation volume to 5,000 rads tumor dose in 5 weeks. The volume is reduced after 5,000 rads tumor dose to encompass the scar with a 3 to 4 cm. margin in all directions. When the total dose exceeds 6,000 rads tumor dose, the field is again reduced to include only the scar. Recently, Suit *et al.*[9] have shown that the local recurrence rate in lesions in the extremities depends upon the grade and size of the primary tumor. Thus, more generous fields are used in the large, high-grade lesions. In view of the recent studies showing the sterilization of subclinical aggregates of tumor with moderate doses of radiation, the total dose has been decreased slightly. Since 1971, 6,000 rads tumor dose in 6 weeks has been used for the low-grade lesions, and 6,500 rads tumor dose in $6\frac{1}{2}$ weeks for the high-grade lesions.

Most of the severe complications (11/17) occurred in patients treated with the tourniquet technique. Since the tourniquet technique offers no advantages in terms of local recurrence rate and has a significant frequency of complications, it has been discontinued.

Most of the radiation complications can be avoided by careful planning. The radiation fields must be planned to give adequate coverage to the surgical bed without including the full circumference of the extremity. When the entire circumference of an extremity is irradiated, a severe, constricting fibrosis may result with varying degrees of edema below the irradiated fields. An entire joint is irradiated only when absolutely necessary, *e.g.*, the rare synovial sarcoma that penetrates the joint space. Whenever possible, the patella should not be irradiated. Extreme care must be used in irradiating the foot in order to preserve its function. The toes, sole of the foot, heel, and the Achilles tendon should not be included in the irradiated fields. If all of these structures must be irradiated, a surgical ablation is better because of the severe complications that may arise from irradiation.

Although the severe complications are rare when proper techniques are used, there is some degree of fibrosis. The reduction in tumor dose from 7,000 rads to 6,000–6,500 rads started in 1971 should decrease the incidence and severity of the fibrosis without increasing the local recurrence rate. Since only 3 of the 100 patients in this series developed lymph node metastasis as a first manifestation of spread of tumor, prophylactic irradiation of the regional lymph nodes does not seem justified.

CONCLUSIONS

A retrospective review of 100 selected patients with soft tissue sarcomas treated by conservative excision and postoperative radiation therapy shows the following:

1. In extremity lesions, a functional limb can be preserved. The 5 year survival rate free of disease is 62 per cent (23/37).
2. The control rate of the soft tissue sarcomas is related to the anatomic site of origin rather than histologic type of the tumor except rhabdomyosarcomas. In lesions of the extremities, the control rate is 82 per cent (51/62).
3. The first manifestation of spread is usually distant metastasis rather than regional lymph node metastasis.
4. The complications can be minimized if sufficient attention is given to the placement of the surgical scar and the radiotherapeutic technique.

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SELECTIVE INTRA-ARTERIAL EMBOLIZATION OF BONE TUMORS*

A USEFUL ADJUNCT IN THE MANAGEMENT OF SELECTED LESIONS

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ALTHOUGH angiography has gained wide acceptance as a radiologic method for the investigation of neoplasms in general, its contribution to bone tumor management, in particular, has not been crucial. An accumulating experience with osseous arteriography has shown that it does not serve as a consistent basis for distinguishing benign from malignant disease. Despite this diagnostic limitation, however, it may still supply significant information in selected cases.[4,14–16]

Angiography, enhanced by vasoactive drugs, magnification and photographic subtraction techniques, may be of great value in defining a bone tumor's intra- and extraosseous extent. It depicts a lesion's degree of vascularity, thereby serving as a guide to suitable sites for biopsy, and it maps the lesion's major peripheral as well as its internal vascular anatomy.

However, in addition to this circumscribed role of cartographer for the surgeon, radiotherapist and pathologist, the angiographer has the potential of making another more dynamic contribution to bone tumor management. By regarding the tumor's vascular network not merely as a maze to be outlined, but as an avenue for therapeutic intervention, he may, *via* the transcatheter approach, selectively suppress the blood supply of certain highly vascular lesions by means of iatrogenic arterial embolization. He may, therefore, with this relatively atraumatic technique furnish an ancillary approach in the management of selected cases.

Therapeutic arterial embolization has been utilized in the management of cerebral arteriovenous malformations, aneurysms,[3,5–9] postbiopsy arteriovenous renal fistulae,[2,12] and in the control of gastrointestinal and post-traumatic pelvic hemorrhage.[1,10,11,13] The currently reported cases, however, represent an initial experience in the attempt to therapeutically embolize peripheral bone tumors.

MATERIAL AND METHOD

All arterial embolizations were performed using the Seldinger technique. A 6 French polyethylene catheter with a .046 inch end hole was introduced percutaneously into the femoral artery over a .045 stainless steel guidewire. A soft curved catheter with a torque guide system and a large bore Tuey adaptor* was used in both cases.

The large bore, thin walled system with good torque control had the dual advantage of facility in selectivity and the ability to transmit large size emboli.

Arteriographies were performed with sodium methylglucamine diatrizoate (Renografin 76). Following the arteriography, the catheter was positioned in the vessel to be embolized. Gelfoam (methylcellulose) strips were cut into 2–3 mm. pieces, soaked in Renografin 76, and forcefully flushed through the catheter directly into the tumor vascular bed. The compressible Gelfoam pellets conform to the contour of the catheter under pressure of injection with a hand held 10 cc. syringe. When the embolus leaves the catheter, it has a tendency to

* Cope System—Elecath. Corp.

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re-expand, and, therefore, has the potential of occluding larger vessels. This process was repeated until all the accessible feeding vessels were embolized. Repeat arteriograms were obtained to verify the extent of ischemia achieved.

Many different materials such as metallic pellets, silastic pellets, fat and fascia, as well as autologous blood clot have been used for embolization. They all have one common disadvantage in that their size must correspond to the inner catheter diameter and that they may fail to embolize small vessels downstream from the catheter tip. An advantage of the metallic or radiopaque pellets is their visibility, allowing the operator better control through a knowledge of the exact current and future placement of the embolus. The latter information is unnecessary when immediate surgery is contemplated. A disadvantage of most of the above-mentioned emboli is that their size must correspond to the inner catheter diameter and that they fail to occlude small vessels downstream from the catheter tip. Autologous clot too may not be permanent in terms of disintegration and lysis.

We have found compressible Gelfoam pellets to be most satisfactory for our purpose. The permanence or long duration of pellets, however, is not vital, when surgery is planned to shortly follow embolization.

REPORT OF CASES

Case 1. AB was a 35 year old male who complained of pain and swelling about both knees. He had had a mass removed from his left fifth metacarpal 6 years prior to admission. A large mass appeared on the lateral aspect of the right leg just distal to the knee which was removed elsewhere 7 months prior to admission. A similar swelling had appeared shortly thereafter in approximately the same place on the left leg. He had sustained a 15 lb. weight loss in the year prior to admission.

Physical examination revealed swelling and limited motion about both knees with tenderness and increased warmth over the anterior medial aspect of the right tibia. A frontal roentgenogram of the knees (Fig. 1) showed the stump of the previously amputated fibula as well as a large, lytic expansile lesion which extended to the subarticular portion of the right tibia and involved the major portion of its proximal shaft. A similar lesion had destroyed the upper third of the left fibula. Both lesions had clear matrices, no mineral within them and were associated with cortical disruptions and soft tissue masses.

His examination was otherwise unremarkable. He had an increased serum phosphorus (5.66 mg. per cent) and alkaline phosphatase (110 mU/ml.), normal serum calcium, and an erythrocyte sedimentation rate of 58 mm./hour. No other primary neoplasms and no evidence of hyperparathyroidism were found. Open biopsy of the left fibula done on March 15, 1972, under general anesthesia, disclosed a large disintegrating mass of yellow, cheesy, fibrinous tissue which appeared to involve surrounding muscle. The tumor was very vascular and hemostasis was difficult to achieve despite a thigh tourniquet inflated to 550 mm. of mercury pressure. The hemorrhage recurred after tourniquet release and appeared to stem from the tumor mass itself. No specific bleeding site could be located, however. Hemostasis was eventually obtained using surgagel and pressure.

Figure 2 shows several of the biopsy fragments consisting of flesh colored hemorrhagic tissue containing occasional blood filled spaces which ranged from 1.3–2.5 cm. in major dimension. Preliminary sections showed the dilated sinusoids and patterns of interstitial extravasation of blood which characterizes the appearance of an aneurysmal bone cyst (Fig. 3*A*). The tissue between the sinusoids, however, was quite cellular, with capricious distribution of giant cells (Fig. 3*B*). The pathologic diagnosis was that of a giant cell tumor with aneurysmal transformation.

Bilateral femoral arteriograms (March 15, 1972) delineated the marked hypervascularity of the huge expansile tumors. Neovascularity was demonstrated in the neighboring soft tissues which the neoplasm had presumably involved. The left fibular lesion appeared to involve the proximal left tibial shaft as well. Both tumor beds were wildly vascular with large aneurysmally dilated arteries and veins, early arteriovenous shunting, and pooling of contrast material (Fig. 4). The right proximal tibia was biopsied under general anesthesia on

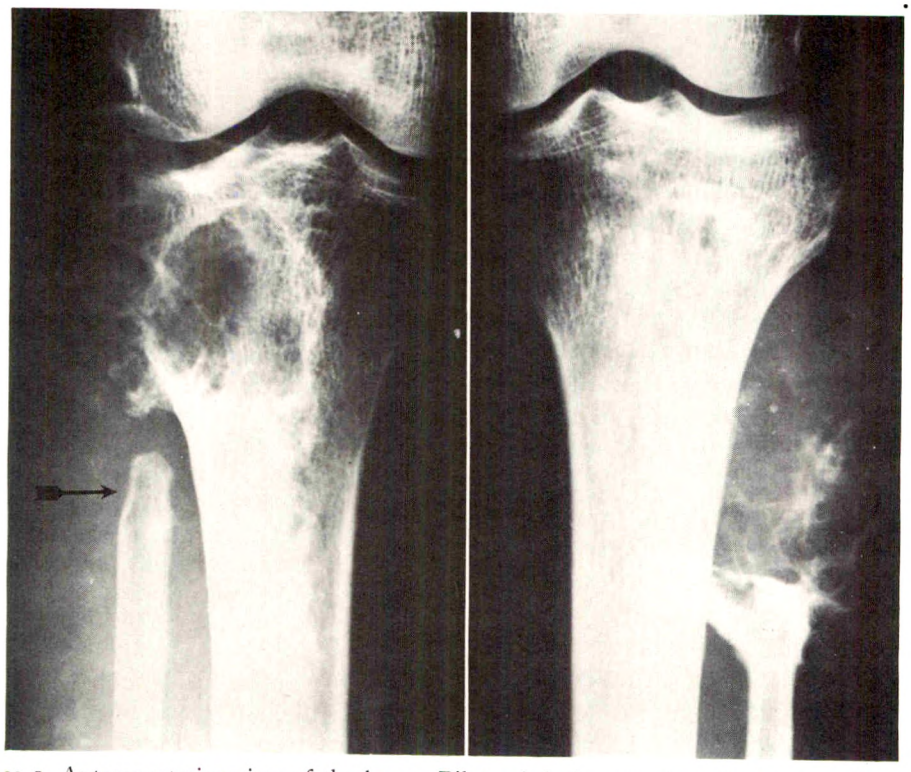


FIG. 1. Case 1. Anteroposterior view of the knees. Bilateral, lytic, nonmineralized, expansile lesions have thinned and partially destroyed the cortices of the superior lateral aspect of the right tibia and the proximal left fibula. The right tibial lesion is eccentrically placed and extends up to the subarticular region. The fibular lesion, too, involves the end of the bone. Note stump of previously resected right fibula (black arrow).

March 29, 1972. Incision through a thin anterior tibial cortex of egg shell consistency revealed a mass of yellowish friable tissue which bled easily. It continued to bleed after tourniquet release necessitating a transfusion of 2 units of blood in the operating room. The pathologic diagnosis was again that of multuple giant cell tumors of bone with superimposed aneurysmal transformation.

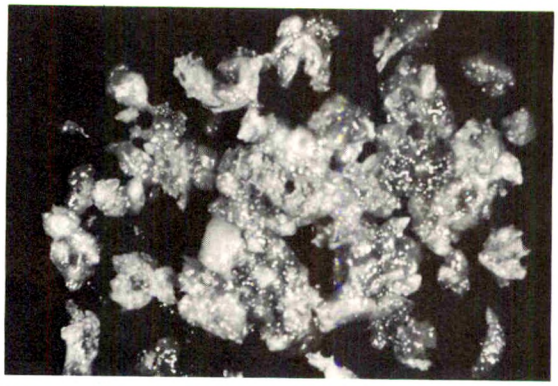


FIG. 2. Case 1. Multiple tissue fragments obtained at the time of open biopsy of left fibular tumor.

Continued work-up revealed no evidence of hyperparathyroidism which would make the occurrence of multiple giant cell tumors more tenable in terms of their representing "brown tumors." There was not, at this time, nor had there previously been, any evidence of a primary neoplasm. The pathologic diagnosis, therefore, continued to be that of multiple giant cell tumors of bone. The practical but overwhelming problem now at hand was that of trying to halt the progressive bilateral massively destructive advance of lesions which had already severely compromised this otherwise able 35 year old male. Salvage was all the more imperative not only in view of his age, but in view of the nature of the lesions which, although locally aggressive, were thought to be biologically benign.

Radiotherapy as the sole treatment appeared contraindicated for this presumably benign

multifocal process, while a questionable effect in terms of decreasing the lesions' vascularity and a stipulated 4 week delay required prior to surgical intervention made irradiation a questionable adjunct.

Therefore, in view of the young age of the patient, the lesions' purported benignity, a history of similar lesions having been removed from the fifth metacarpal and the right fibula, with no recurrence and no known primary neoplasm, the orthopedist decided upon the heroic undertaking of resecting both lesions. The imposing technical problems involved not only the preservation of the patient's lower extremities and his ability to walk despite the lesions' size and the massive resections required to remove them, but also included their known marked hypervascularity. The latter was documented angiographically as well as clinically on the occasion of 2 previous biopsies when, despite the application of tourniquets, hemostasis was difficult to achieve. For these very same reasons, this patient was considered an excellent candidate for preoperative, selective embolization of the tumors' major arterial supply.

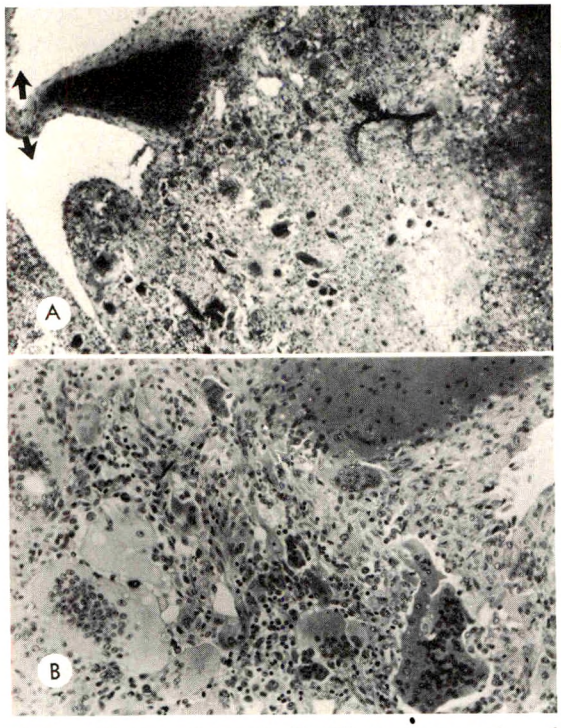


Fig. 3. Case 1. (*A* and *B*) Photomicrographs of histologic sections of left fibular tumor. (*A*) The dilated sinusoids which characterize the appearance of an aneurysmal bone cyst (black arrows) are visible. Note the interstitial extravasation of blood as well as the giant cell containing cellular tissue interspersed between the sinusoids. (*B*) There is a more numerous distribution of giant cells in another section of the lesion. The pathologic diagnosis was that of giant cell tumor with aneurysmal transformation.

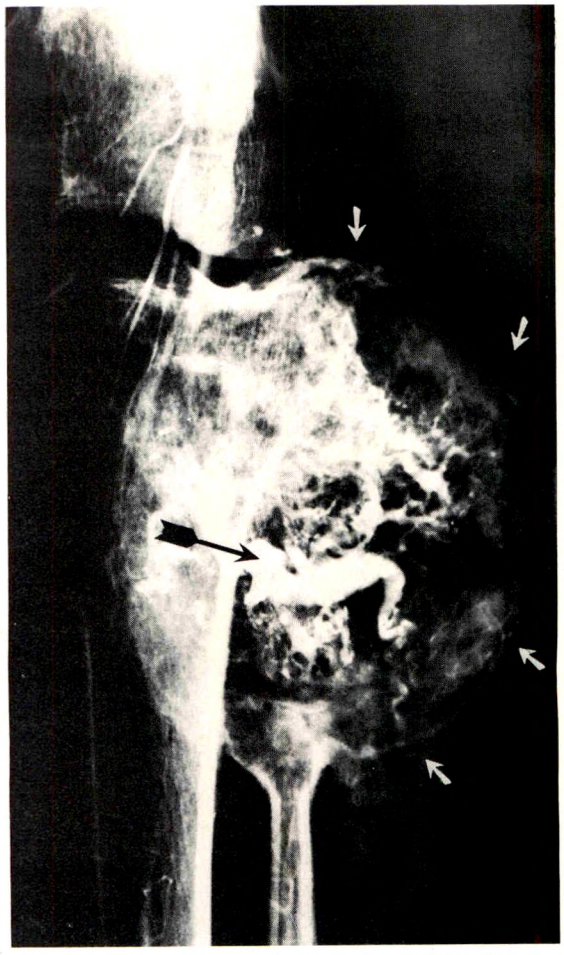


Fig. 4. Case 1. Anteroposterior view of arteriogram of left fibular tumor, arterial phase. A wild tangle of arteries and veins is delineated within the tumor bed. Note pooling of contrast medium and early filling of a large, aneurysmally dilated vein (black arrow), as well as the massive extraosseous extent of the lesion (white arrows).

Accordingly on March 28, 1972, a left superficial femoral arteriogram which served to reoutline the vascular supply of the left fibular tumor (Fig. 5*A*) was followed by consecutive selective catheterization of several of its feeding vessels and their selective occlusion with Gelfoam emboli. Occlusion was accomplished

by means of 2 mm. to 3 mm. sized Gelfoam pellets which were presoaked in Renografin 76 and flushed through the catheter into the preselected tumor vessels. A subsequent femoral arteriogram demonstrated the occlusion of several of the major vessels supplying the tumor mass (Fig. 5*B*).

A repeat left femoral arteriogram on April 12, 1972, just prior to surgery, revealed that the embolized vessels remained occluded with continued diminished vascularity of the tumor bed. Other vessels supplying the area, however, appeared to have hypertrophied since the previous examination. The patient was immediately taken to the operating room where he underwent an *en bloc* resection of the left fibular head along with a portion of the posterolateral upper tibia which the tumor had partially invaded. The pneumatic tourniquet was released after 2 hours and 5 minutes of ischemia time. Good pulsations were noted in the posterior tibial artery. Hemostasis was readily achieved using clamp and cautery.

The entire mass of muscle, connective tissue and tumor which surrounded and involved the proximal segment of fibula measured 21×8 cm. (Fig. 6). The tumor itself was flesh colored and friable. Its more solid portions, enforced by fibrous tissue, were perforated by dilated sinusoids ranging from 0.2 to 1 cm. in diameter. The spongiosa of the neighboring tibial segment did not appear grossly invaded by tumor. Representative sections again showed the mixed patterns of giant cell tumor and aneurysmal bone cyst, the latter represented by dilated sinusoids and a great deal of focal interstitial hemorrhage.

Embolization of the contralateral right tibial tumor was performed on May 1, 1972. It was planned to coordinate with the time of operative intervention, since the duration and degree of the resultant Gelfoam arterial occlusion was uncertain.

A right popliteal arteriogram demonstrated 2 major feeding arterial branches supplying the lesion (Fig. 7*A*). Following embolization, there was complete occlusion of the upper feeder; *i.e.*, the lateral inferior geniculate artery which arose from the popliteal artery just behind the knee joint (Fig. 7*B*). The second feeder arising from the proximal anterior tibial was also partially occluded. The postembolization arterio-

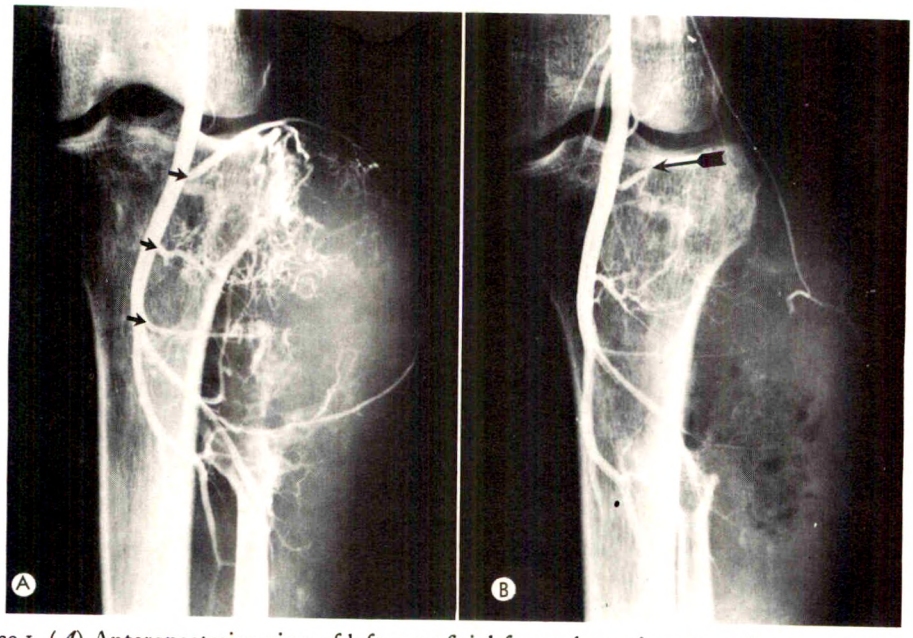


FIG. 5. Case 1. (*A*) Anteroposterior view of left superficial femoral arteriogram, prior to embolization of left fibular tumor; arterial phase. The popliteal artery and several of its branches constitute major sources of vascular supply for the lesion (arrows). (*B*) Anteroposterior view of repeat left superficial femoral arteriogram, postembolization; arterial phase. Note the sharp termination of the embolized lateral inferior geniculate artery (arrow) with the resulting diminished vascular supply to the tumor bed. Air in soft tissues is related to previous biopsy.

gram revealed a markedly decreased amount of contrast medium within the tumor mass with normal arterial flow to the lower extremity (Fig. 7*B*). Therefore, embolization was successful in significantly and selectively decreasing blood flow to this tumor mass.

Embolization was followed on May 8, 1972, by an *en bloc* resection of the deep tissues of the right upper leg which included the anterior, lateral and part of the posterior compartments (Fig. 8). Despite the size of the resection, comparatively little blood loss was encountered.

Case II. November 1, 1971, was the second CPMC admission of a 53 year old male, who complained of knee pain, numbness of the right anterior thigh and a painful swelling about the right hip for several weeks. His first admission 6 years prior had been for relief of 2 subdural hematomas.

A skeletal survey disclosed a large lytic lesion in the right ilium associated with cortical destruction and a fracture through the anterior superior iliac spine (Fig. 9). An elevated alkaline phosphatase (90 mU/ml.) and SGOT (103 mU/ml.) were noted. Intensive investigation yielded no primary focus.

Fig. 6. Case 1. Specimen of *en bloc* resection of proximal left fibula including soft tissue extension of the tumor.

Abdominal arteriography further defined a very vascular lesion which had extended beyond the ilium into the soft tissues of the right buttock and had displaced the cecum and ureter to the left. There was suggestive evidence of a metastatic deposit within the right lobe of the liver.

An open biopsy on November 4, 1971, revealed a large, 10×12 cm., necrotic mass which extended retroperitoneally, displaced the cecum and ureter to the left and yielded adenocarcinoma cells.

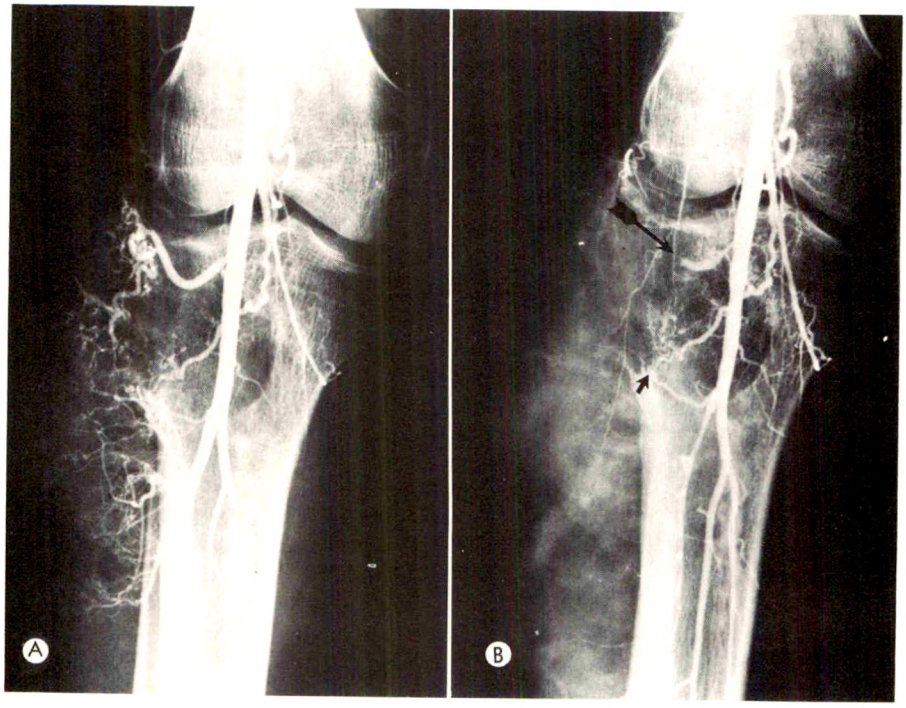
Radiation was administered with a cobalt 60 source to a total tumor dose of 4,000 rads in 4 weeks. After an approximate 50 per cent decrease in the lesion's size, it was selectively perfused with methotrexate *via* a catheter placed in the third right lumbar artery. An extensive rash, mucous membrane irritation, moniliasis and a precipitous drop in white blood cell count forced the discontinuance of chemotherapy after 6 days of intra-arterial perfusion. Another course of chemotherapy with cytoxan was subsequently given.

His fifth admission on July 24, 1972, was for increasing swelling about the hip and flank and for pain which required narcotics. Roentgenograms showed an increase in the area of iliac bone destruction and in the size of the associated soft tissue mass with further retroperitoneal extension.

In view of the increasing size of the mass, the severe pain, the course of radiotherapy and the 2 previous courses of chemotherapy with concomitant diminished resistance, it was felt that perhaps selective arterial embolization of the lesion should be attempted with a view towards palliation.

Accordingly, an aortogram was obtained on August 2, 1972, which revealed that the 4th lumbar artery and branches of the hypogastric artery were the lesion's major vascular feeders (Fig. 10) and these were selectively embolized.

Postembolization arteriography demonstrated a marked decrease in blood flow to the tumor (Fig. 11, *A* and *B*; and 12, *A* and *B*). Transient severe pain in the right buttock and leg, together with mild temperature elevation developed on August 3, 1972. By August 6, 1972, however, there was a definite decrease in the



size of the pelvic mass, as well as an associated decrease in its heat and tenderness.

Embolization, therefore, afforded temporary relief in the form of decreased pain and a decrease in the size of the mass in the remaining months left to this patient. He succumbed on October 11, 1972, as a result of metastases to the spinal cord.

DISCUSSION

Therapeutic embolization was carried out with totally different intent in these 2 patients. In Case 1 it was utilized as an operative adjunct designed to diminish the potential hazard of exsanguinating hemorrhage and, thereby, to facilitate the planned resection of highly vascular lesions. In Case 11, it was employed as a relatively atraumatic palliative procedure in a patient whose poor condition mitigated against any further conventional intervention, and suggested that therapeutic embolization may

FIG. 8. Case 1. Specimen of *en bloc* resection of right tibial tumor which included the anterior, lateral and part of the posterior compartments of the soft tissues of the leg.

Fig. 7. Case I. (*A*) Anteroposterior view of right superficial femoral arteriogram, pre-embolization. Two branches of the popliteal artery and one branch of the anterior tibial artery are major contributors to the tumor's arterial supply. (*B*) Anteroposterior view of repeat right superficial femoral arteriogram, post-embolization. The right lateral inferior geniculate artery has been completely occluded by a Gelfoam embolus (large arrow). Note partial occlusion of another feeding vessel arising from the anterior tibial artery (small arrow) as well as the over-all decrease in the tumor's vascularity.

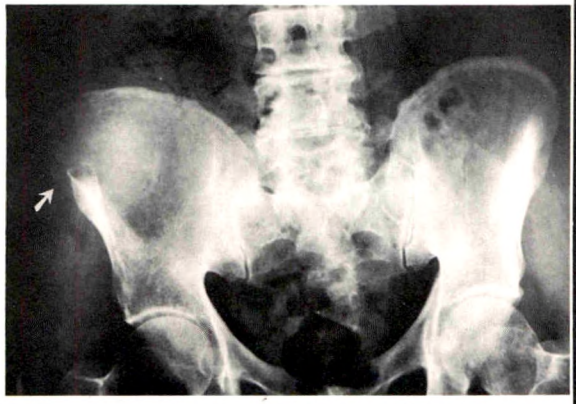


Fig. 9. Case II. Anteroposterior view of pelvis shows a large destructive lesion of the right ilium which has disrupted its cortex and fractured through the anterior superior spine (arrow).

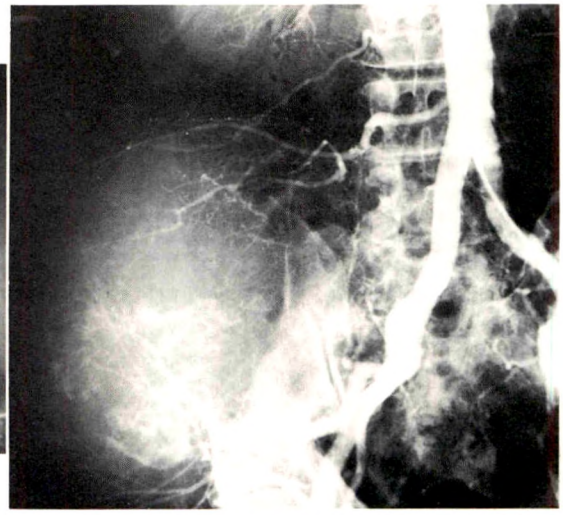


Fig. 10. Case II. Anteroposterior view of aortogram demonstrates that branches of the 4th lumbar and hypogastric arteries supply the tumor. The large extraosseous extent of the lesion is now better delineated.

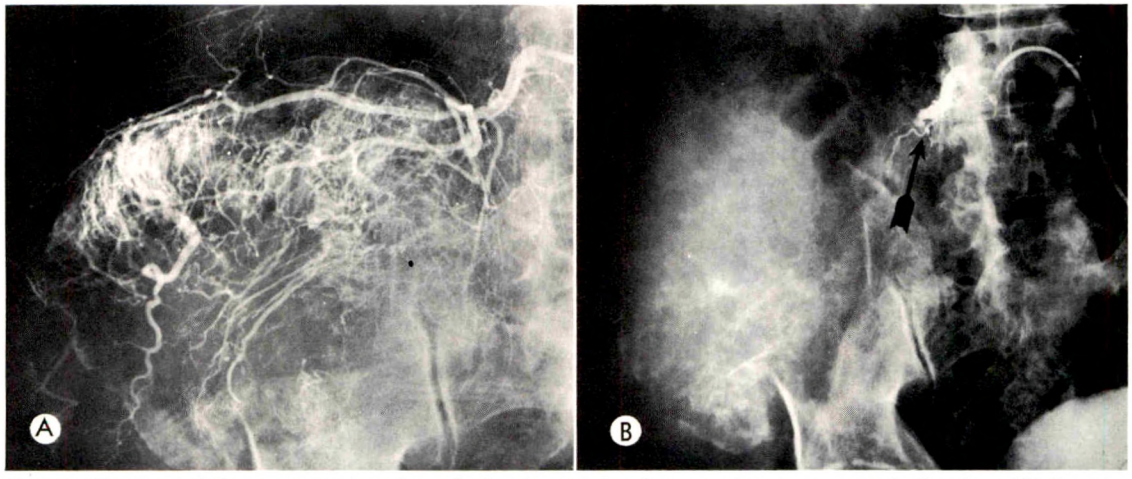


Fig. 11. Case II. (*A*) Anteroposterior view of selective 4th lumbar arteriogram, pre-embolization. (*B*) Anteroposterior view of selective 4th lumbar arteriogram, postembolization. Note complete obliteration by Gelfoam embolus (arrow) and dramatic decrease in the arterial supply to the superior portion of the mass. A faint blush of contrast material inferiorly attests to collateral circulation.

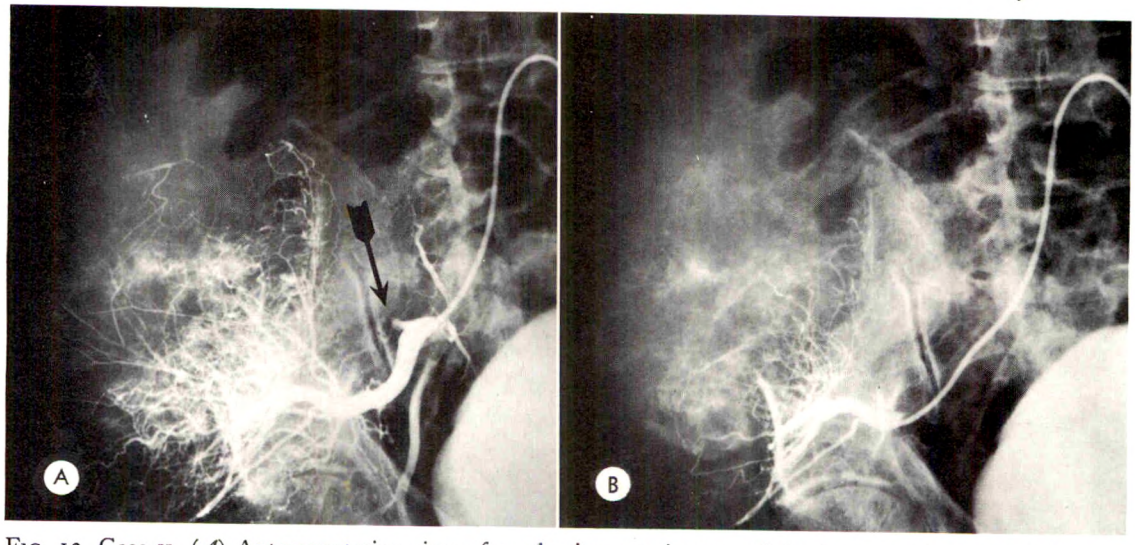


FIG. 12. Case 11. (*A*) Anteroposterior view of a selective arteriogram of the hypogastric artery delineates another major contributor to the tumor's vascular supply. Note abrupt termination of an arterial branch which has just been occluded (arrow). (*B*) Additional Gelfoam emboli have now partially occluded other vessels supplying the inferior portion of the lesion.

render a tumor more manageable clinically as well as surgically.

This preliminary report appeared warranted in view of its promise as evidenced in Case 1, and secondly, to arouse the interest of diagnostic radiologists as well as angiographers and surgeons, who may become involved in the selection of patients for a procedure whose further clinical application may prove beneficial.

SUMMARY

Our initial experience with therapeutic selective arterial embolization of 3 highly vascular bone tumors is discussed.

In 2 benign lesions embolization of Gelfoam particles through a large bore selective catheter facilitated complete resection by limiting hemorrhage at the time of surgery.

Embolization of a vascular malignant tumor provided temporary palliation.

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THE TUMBLING BULLET SIGN IN A POST-TRAUMATIC BONE CYST*

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ALTHOUGH roentgenographic criteria for the recognition of unicameral bone cysts are well established, they do not always serve to definitively distinguish other similarly situated solid radiolucent lesions. In addition, the etiology and evolution of unicameral bone cysts are still unsettled despite their acceptance as a pathologic entity for many decades.

The following case of a 15 year old male who developed a bone cyst as a result of a bullet wound is, therefore, of dual interest; first from the pathogenetic point of view in that its evolution was documented as a corollary of trauma; and secondly, from the roentgen diagnostic point of view in that free movement of the foreign body within the confines of the lesion established its cystic rather than solid nature.

REPORT OF A CASE

A 15 year old white male was seen in the emergency room 2 hours after sustaining a gunshot wound of the right knee. The bullet had entered his thigh laterally and had lodged in the medullary cavity of the distal femur (Fig. 1). There was no gross evidence of fracture or of a cystic lesion at the site. Fibrous cortical defects of the femur and tibia were incidentally noted. The wound was debrided in the operating room and irrigated with saline and penicillin. An additional 5,000,000 units of aqueous penicillin were given intravenously.

Sixteen months later, he complained of a painless clicking sensation and locking of his right knee. Roentgenograms revealed that the bullet, although still lodged in the distal femur, was now surrounded by a large, oval shaped, well demarcated lucent area within which it appeared to change position (Fig. 2, *A* and *B*). Additional roentgenograms with the femur elevated perpendicular to the horizontal plane (Fig. 3) demonstrated that the bullet moved freely to the most dependent portion of the lesion with each change in position. A persistent dull ache about the knee prompted a second operative intervention 5 months later, although the lesion had not increased in size.

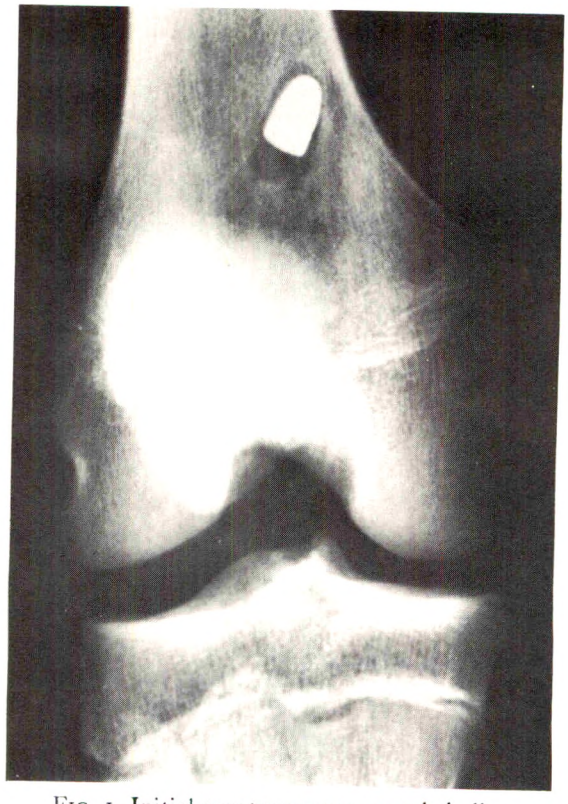

FIG. 1. Initial roentgenogram reveals bullet within shaft of the right femur.

At surgery a 4×6 cm. cyst in the centeromedial aspect of the distal femur was found to contain a "machinery oil like" fluid and a bullet. The latter was retrieved and the cyst wall, which was approximately 0.5–1 mm. thick, was thoroughly curetted. There was no evidence of infection. The cavity was irrigated with oxacillin and packed with bone chips.

Microscopically, the membrane was composed of histiocytic cells and scar tissue which ac-

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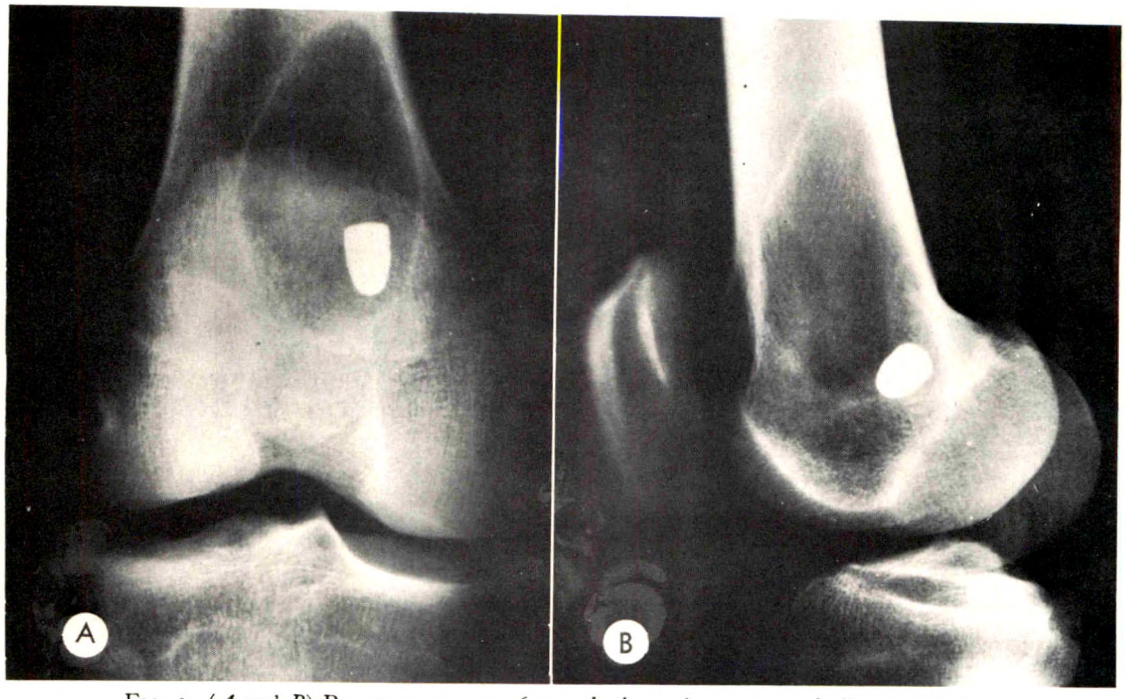

Fig. 2. (*A* and *B*) Roentgenograms 16 months later demonstrate bullet at inferior margin of a large radiolucent lesion with well defined margins.

commodated focal aggregates of lymphocytes and plasma cells. Several reactive new bone spicules, fibrous tissue and a few fragments of dead bone were also noted. There was no evidence of osteomyelitis.

Cultures of the cyst fluid were unremarkable. Cell count revealed 1.1 million red blood cells and 300,000 white blood cells per mm.^{3}. The patient received oxacillin and ampicillin and was placed in a long leg cast.

DISCUSSION

The currently reported lesion satisfied both the roentgen and pathologic criteria for a simple or unicameral bone cyst. Unicameral bone cysts are most commonly clinically occult unless fractured, with no consistently associated biochemical or physical abnormalities.[3] They may be initially diagnosed by the radiologist on the basis of a combination of "classic findings." These include the presence of a centrally located radiolucent metaphyseal lesion in a long bone of a young child. The cyst commonly thins and expands the cortex symmetrically with its base oriented towards the growth plate, occasionally simulating a truncated cone. Its transverse diameter usually does not exceed that of the growth plate.[5] Two-thirds of the lesions have been found in the proximal humerus and distal femur.[3]

Although common, these classic criteria are inconstant and, more significantly, are not pathognomonic. Similar roentgen characteristics may be shared by such solid intramedullary lesions as fibrous dysplasia and enchondroma which, also, may be solitary, radiolucent and metaphyseal in location. The free fall of a radiopaque body within the confines of such a lesion, therefore, provides an important clue as to its internal architecture. The diagnostic implications of a foreign body moving within a hollow or fluid filled structure have previously been discussed in relation to retroperitoneal abscesses[6] and as a sign of intravenous migration, while the changing position of a segment of fractured cortex has proved useful in the diagnosis of unicameral bone cyst.

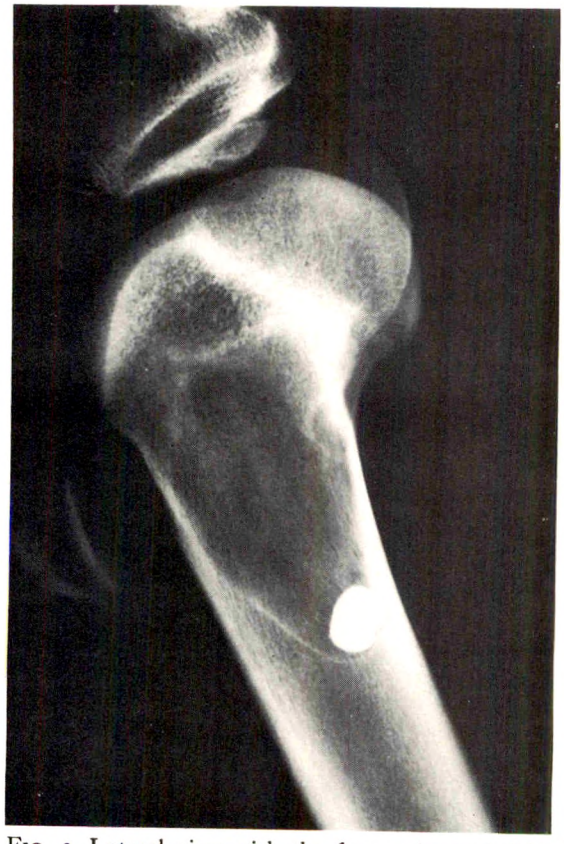

FIG. 3. Lateral view with the femur elevated. The bullet now falls to the superior margin of the lesion, which in this position becomes its most dependent portion, thereby demonstrating its cystic nature.

The current case is unique in that a bullet entered the medullary cavity without splintering or obviously fracturing the cortex and remained to serve as a reliable sign of the cystic nature of the resultant lesion. Whether it is a bullet in an abscess cavity,[6] a bone fragment falling to the dependent portion of a cyst or, as in the above case, a bullet falling freely within a fluid filled post-traumatic bone cyst, the principle of the "Tumbling Bullet" or "Fallen Fragment"[8] is a simple one; *i.e.*, that of a heavier object being able to move freely in a lighter environment.

The current case, however, is of further interest in documenting the post-traumatic evolution of a unicameral bone cyst, and thereby substantiating one of the theories of its pathogenesis. The development of a bone cyst from the time of its inception has rarely been observed. Two cases reported by Broder[1] appeared to develop at the site of pre-existing osseous abnormalities, which roentgenographically had the appearance of nonossifying fibromas or calcified cartilage rests. One of these lesions was eccentrically placed. Neither patient had sustained trauma.

Pommer[7] proposed that the solitary bone cyst results from a focus of intramedullary hemorrhage which then becomes encapsulated. Continued transudation of fluid into the cyst with increasing internal pressure was held responsible for erosion of neighboring trabeculae and continued cortical expansion. Since an ordinary fracture with cortical and periosteal disruption presumably prevents the formation of a closed pressure system, the possibility of mild trauma without fracture but with intramedullary hemorrhage was entertained as an etiologic possibility. By the same token, unicameral bone cysts have been noted to heal or fill in after spontaneous fracture.

Although Cohen's more recent theory[2] suggests a relationship between fluid accumulation and occlusion of a sinusoidal vessel on the basis of trauma and/or thrombosis, he felt that trauma alone was an insufficient etiologic factor.

Developmental anomalies of microscopic sized vessels have also been suggested to explain both the development and predominantly metaphyseal localization of these lesions. This concept envisages an abnormal proliferation of sinusoidal vessels in the rapidly remodelling metaphyseal zone. Resultant inadequate communication with the vascular system might coincidentally result in an increased susceptibility of these vessels to partial block or occlusion after minimal trauma. An obstacle to the normal drainage of interstitial fluid is, therefore, postulated which may be aggravated by trauma. These speculations could account for one consistent characteristic of bone cysts; *i.e.*, their metaphyseal predilec-

tion, while the currently reported case has established an instance where trauma could be directly incriminated.

SUMMARY

Various hypotheses for the etiology of unicameral bone cysts are discussed.

The unique documentation of a lesion which developed as a result of a bullet wound appears to lend credence to trauma as an inciting agent.

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PRIMARY IMMUNODEFICIENCY DISEASES AND MALIGNANCY*

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PRIMARY immunodeficiency diseases comprise a group of disorders with defects in humoral and/or cell-mediated immunity caused by various pathophysiological mechanisms. Elucidation of the constituents and functions of the immune system has progressed at a rapid pace in recent years. This has led to an appreciation that the immune system plays an important role in oncogenesis, although the causal mechanisms are far from clearly understood. Immunosuppressed transplant recipients are known to have an unusually high incidence of malignancy.[18,21] Among the most convincing evidence which indicates an association between immunity and oncogenesis is a dramatically increased incidence of malignant disease in the primary immunodeficiencies.[6,7,12–14,23]

It has been estimated that the incidence of malignancy in these disorders is approximately 10,000 times greater than in the general population of comparable age.[7] This figure is probably erroneously high: a more recent study estimated the risk of death from malignancy in children under 15 years of age with primary immunodeficiency diseases to be 100 times greater than that of the general age-matched population.[14] The Immunodeficiency-Cancer Registry has recently been established to facilitate the collection of data and to study these patients.[13]

The purpose of this paper is to describe 4 children with primary immunodeficiency diseases who developed fatal malignancies and to call to the attention of radiologists the association of these conditions.

PRIMARY IMMUNODEFICIENCIES

For a complete classification and discussion of the primary immunodeficiency diseases, the reader is referred to other sources.[4,5,8] The major disorders are briefly reviewed here, with special reference to the occurrence of malignancy. Table 1 summarizes the estimated risk and types of malignancy in each condition.

Infantile X-linked agammaglobulinemia (*Bruton-type*) is a recessive disorder occurring only in males, with an isolated defect in humoral immunity. Cellular immunity is normal. Serum immunoglobulin levels are extremely low. These children are plagued with recurrent infections caused by pyogenic bacteria, and *Pneumocystis Carinii* pneumonia is not uncommon. Most viral infections are handled adequately. Lymph nodes are small, with a paucity of plasma cells and germinal centers. The thymus is normal. Thus far leukemia has been almost the only type of malignancy reported in this disorder, the exception being a single case of lymphoma.[13]

It is now well established that the thymus plays a key role in the development of cellular immunity, which mediates homograft rejection, delayed hypersensitivity, and graft-versus-host reaction.

In the *III–IV pharyngeal pouch syndrome* (*Di George's syndrome*) there is an isolated defect in cellular immune response secondary to absence or hypoplasia of the thymus. The parathyroids, derived as the thymus from the 3rd and 4th pharyngeal pouches, are also absent, leading to neonatal tetany. Viral and fungal infections and *Pneumocystis Carinii* pneumonia are frequent, severe, and often fatal. There have been few reports of this condition and no reported cases of malignancy.

Severe combined immunodeficiency refers

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TABLE I

ESTIMATED RISK AND TYPES OF MALIGNANCY IN THE PRIMARY IMMUNODEFICIENCY DISEASES[13]

Disease	Incidence of Malignancy*	Estimated Risk of Malignancy (Per Cent)	Types of Malignancy
Infantile X-linked agammaglobulinemia	6/approx. 100	6	Lymphoreticular malignancy and leukemia
III–IV Pharyngeal pouch syndrome	None reported	—	
Severe combined immunodeficiency	9/approx. 400	2	Lymphoreticular malignancy and leukemia
Common variable immunodeficiency	41/approx. 500	8	Lymphoreticular malignancy predominates, 29 per cent nonlymphoid (nearly half of these are gastric carcinoma)
Ataxia-telangiectasia	52/approx. 500	10	Lymphoreticular malignancy and leukemia predominate, 11 per cent nonlymphoid
Wiskott-Aldrich syndrome	24/approx. 300	8	Lymphoreticular malignancy predominates
Selective IgA	Not established	—	Epithelial malignancy predominates, especially gastrointestinal carcinoma

* Based on cases of malignancy known to the Immunodeficiency-Cancer Registry as of May 1, 1973, and estimates by several participating physicians of the size of their immunodeficient patient populations.[13]

to at least 4 types of inherited immunodeficiency disorders whose immunologic status is essentially the same.[8] There are severe defects in both humoral and cellular immunity, and untreated patients usually die in the first year of life. In recent years bone marrow transplantation has led to successful immunologic reconstitution in some patients. At least 9 cases of malignancy have occurred in association with severe combined immunodeficiency, and as in infantile X-linked agammaglobulinemia they have all been leukemia or lymphoreticular neoplasms.[13]

Common variable immunodeficiency is in reality a heterogeneous group of disorders which represents one of the most common forms of immunodeficiency in the general population. Onset of clinical manifestations may begin anywhere from infancy to adulthood. Variable deficiencies in any or all classes of immunoglobulins are present. Cell-mediated immunity is intact early but usually becomes deficient late in the course of the disease. Affected individuals have an increased incidence of gastrointestinal disorders, including diarrhea, protein-losing enteropathy, malabsorption and *Giardia lamblia* infestation. A common but not invariable finding in variable immunodeficiency is lymphoid hyperplasia. Enlarged lymph nodes are frequently present, as well as nodular lymphoid hyperplasia of the gastrointestinal tract.[11] The latter is particularly prevalent when serum IgA is low or absent.[1] The incidence of malignancy is markedly increased. In contrast to infantile X-linked agammaglobulinemia and severe combined immunodeficiency, many types of malignant neoplasms occur. Twenty-nine per cent of all tumors are nonlymphoid, with gastric carcinomas comprising nearly half of this category.[13]

Ataxia-telangiectasia is an inherited disorder characterized by progressive cerebel-

lar ataxia, ocular and cutaneous telangiectasia and recurrent sinopulmonary infections. Onset of the disease is in early childhood, heralded by ataxia. Survival beyond childhood is rare. The thymus is either rudimentary or absent, and peripheral lymphoid tissue is poorly developed. There are defects in both humoral and cellular immunity. About half of these patients have low or absent levels of serum IgA. IgE levels are frequently low. Malignancy occurs with a higher frequency in this disease than in any of the primary immunodeficiencies. As in the other disorders lymphoreticular tumors and leukemia predominate, but approximately 11 per cent of tumors are of nonlymphoid type.[13]

The *Wiskott-Aldrich syndrome* is an X-linked recessive disease with a classic triad of thrombocytopenia, eczema, and severe recurrent infections with all classes of organisms. Affected individuals seldom survive beyond puberty. The nature of the immunologic defect is unknown, but cellular and humoral immunity are both affected. Serum IgM levels are characteristically very low, while IgG levels are usually normal. IgA levels may be normal or elevated. Nearly 1 in 10 children with the Wiskott-Aldrich syndrome die with malignancy, and lymphoreticular tumors occur almost exclusive of all other neoplasms.[13] A feature of this disease is marked generalized lymphadenopathy which may be present for years, with or without subsequent development of lymphoreticular malignancy.[6,7]

Selective IgA deficiency is a relatively common disorder, occurring in the general population with an incidence that has been estimated at from 1 in 700 to 1 in 3,500.[5] A clear-cut pattern of inheritance has not yet been defined. Affected individuals may be asymptomatic or may have an increased incidence of sinopulmonary and gastrointestinal infections. They also exhibit a higher than normal frequency of autoimmune diseases such as rheumatoid arthritis, thyroiditis, lupus erythematosus and pernicious anemia. The incidence of malignancy in this disorder has not been established. Of the recorded cases, however, epithelial neoplasms predominate, particularly those arising in the gastrointestinal tract.[13] It is of further interest that IgA deficiency, either isolated or as a feature of another primary immunodeficiency disease, has been associated with gastric carcinoma in at least 6 cases.[5]

MATERIAL

Four children under 16 years of age with primary immunodeficiency disease and malignancy are reported. Three of the children (Cases I–III) were seen at St. Louis Children's Hospital and 1 (Case IV) was evaluated at Wilford Hall USAF Medical Center. The extent of work-up of the immunodeficiency was variable. All patients expired and in all cases an autopsy was performed. Cases I[3] and II[9] have been reported previously. Case II was reported as a patient with infantile X-linked agammaglobulinemia, but in view of documented abnormality in cellular immunity it is more likely that this patient had common variable immunodeficiency. Case III had classic clinical and autopsy features of ataxia-telangiectasia. Case IV is reported in detail. The clinical features of the reported cases are summarized in Table II, and the roentgenologic features are demonstrated in Figures 1–4.

REPORT OF A CASE

CASE IV. An 8 year old white male was admitted to the hospital in 1965 with diffuse Staphylococcal pyoderma secondary to varicella. At the time of admission he was continuing to develop new varicella skin lesions 2 weeks after onset of his illness. He had had repeated febrile episodes as an infant. As least 5 previous episodes of pneumonia had been documented. Microcephaly and marked mental retardation had been present since early in life. Three siblings also had microcephaly, one of whom has "hypogammaglobulinemia," and a fourth sibling was normal.

He responded to medical therapy including antibiotics and large doses of gamma globulin. The latter was given because of suspected

TABLE II

CLINICAL FEATURES OF REPORTED CASES OF PRIMARY IMMUNODEFICIENCY AND MALIGNANCY

Case	Sex	Immunodeficiency Disease	Humoral Immunity	Cellular Immunity	Type of Malignancy	Age at Time of Diagnosis of Malignancy	Interval between Diagnosis of Malignancy and Death
I	Female	Ataxia-telangiectasia	IgA ↓ IgG normal IgM normal	Negative Monilia skin test. Inability to sensitize to dinitrochlorobenzene	Reticulum cell sarcoma	29 mo.	1 mo.
II	Male	Probable common variable immunodeficiency	IgA absent IgG ↓ IgM ↓ Positive Schick test after immunization. Isohemagglutinin titers absent	Positive histoplasmin skin test. Negative mumps skin test (history of parotitis). Inability to sensitize to dinitrochlorobenzene	Hodgkin's disease	11 yr.	7 mo.
III	Male	Ataxia-telangiectasia	IgA ↓ IgG normal IgM normal	Diminished lymphocyte response to phytohemagglutinin	Lymphocytic lymphoma	7 yr.	14 mo.
IV	Male	Common variable immunodeficiency	IgA absent IgG ↓ IgM ↑	Rudimentary (2 gm.) thymus at autopsy with absent Hassell's corpuscles. Positive histoplasmin skin test	Adenocarcinoma of stomach	15 yr.	2 mo.

immunologic deficiency. Serum protein electrophoresis revealed total protein 7.2 gm. per cent with albumin 60 per cent, alpha—1 globulin 4 per cent, alpha—2 globulin 11 per cent, beta globulin 10 per cent, and gamma globulin 15 per cent.

In succeeding years he was repeatedly treated for pneumonia and suppurative skin infections. Serum protein immunoelectrophoresis was performed in 1968, but the results are unavailable. On the basis of those results, immunodeficiency was diagnosed and he was started on prophylactic gamma globulin injections.

In 1972, at the age of 15 years, he was admitted to the hospital for evaluation of progressive weight loss over the preceding year, totaling approximately 10 kg. He had become markedly weaker during the month prior to admission, with complaints of upper abdominal pain, anorexia and inability to retain oral fluids. Physical examination disclosed a cachectic, microcephalic 27 kg. boy who was markedly mentally retarded. There were numerous cutaneous scars from previous infections. A questionable left upper quadrant mass was palpated.

Complete blood cell count revealed a white blood cell count of 7,200 with normal differential, hematocrit 38 per cent, hemoglobin 12 gm. per cent, and adequate platelets on peripheral smear. *Giardia lamblia* cysts were seen in 3 stool samples. Intermediate strength PPD and coccidioidin skin tests were negative. A histoplasmin skin test showed 3 and 7 mm. of induration at 24 and 72 hours, respectively.

Barium enema examination reportedly showed a mass involving the transverse colon. An upper gastrointestinal series showed findings suggesting a malignant process involving the stomach. On the fifth hospital day he had a generalized seizure, followed by a second convulsion 24 hours later. During the postictal period a definite upper abdominal mass was palpated. At this point he was referred for the first time to Wilford Hall USAF Medical Center.

On admission, in addition to the previously described physical findings, 2+ pitting edema of the left upper and lower extremities was noted, and small axillary, inguinal and supraclavicular lymph nodes were palpated. Serum protein electrophoresis revealed total protein 6.3 gm. per cent with albumin 49 per cent, alpha—1 globulin 11 per cent, alpha—2 globulin 18 per cent, beta globulin 10 per cent and gamma globulin 11 per cent. Immunoglobulin

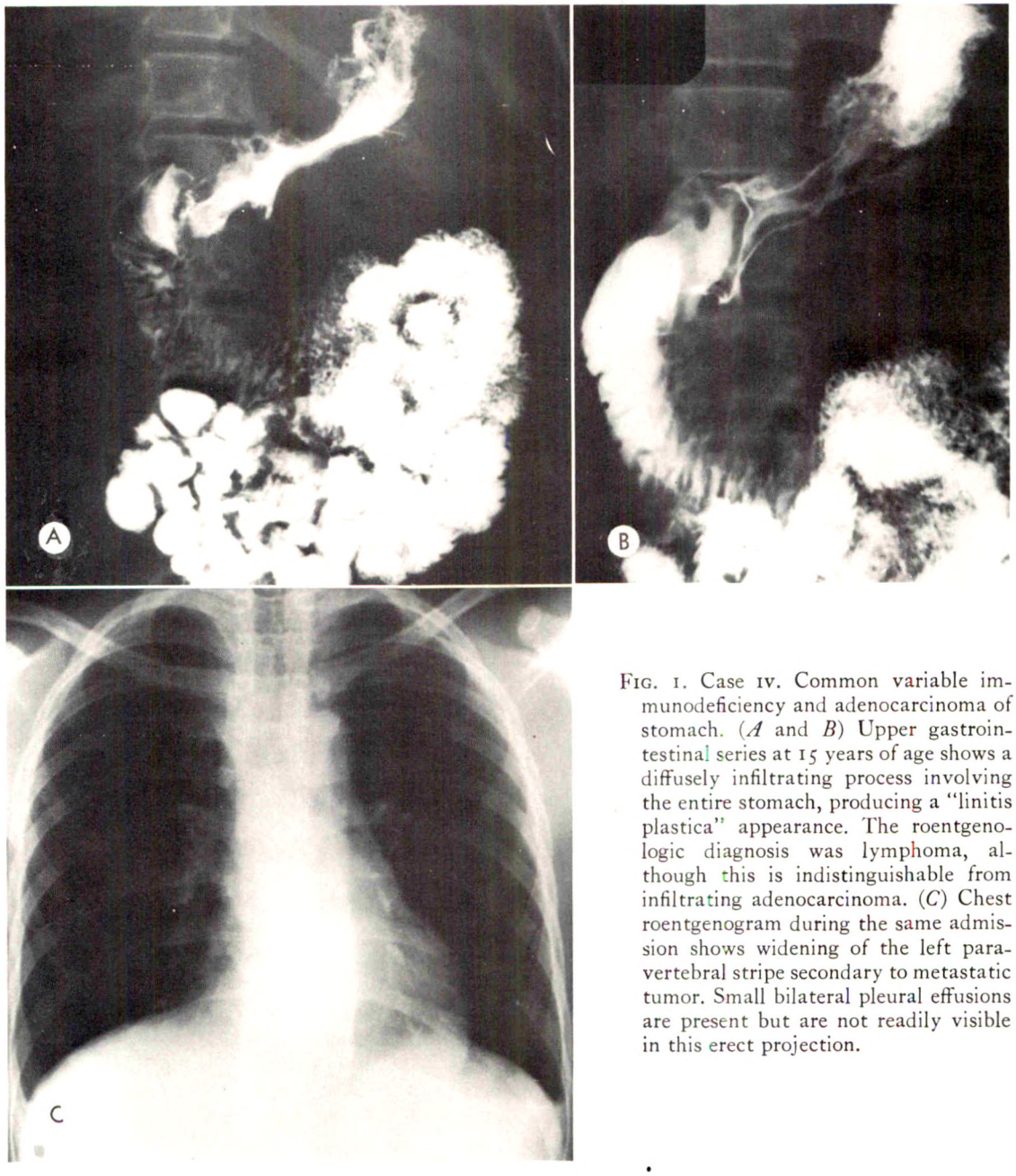

FIG. 1. Case IV. Common variable immunodeficiency and adenocarcinoma of stomach. (*A* and *B*) Upper gastrointestinal series at 15 years of age shows a diffusely infiltrating process involving the entire stomach, producing a "linitis plastica" appearance. The roentgenologic diagnosis was lymphoma, although this is indistinguishable from infiltrating adenocarcinoma. (*C*) Chest roentgenogram during the same admission shows widening of the left paravertebral stripe secondary to metastatic tumor. Small bilateral pleural effusions are present but are not readily visible in this erect projection.

levels were IgG 20 mg. per cent, IgA 0 mg. per cent, IgM 1,036 mg. per cent, and IgD 8.2 mg. per cent. Repeat upper gastrointestinal series revealed a process diffusely involving the stomach, with contraction and rigidity of the wall and destruction of the mucosa (Fig. 1*A*). Chest roentgenography showed widening of the left paravertebral stripe (Fig. 1*B*). The roentgenographic findings were interpreted as being due to primary malignancy of the stomach, most likely lymphoma, with paraspinal extension of tumor into the thoracic cavity. Cerebral angiography revealed an avascular mass in the left temporoparietal area.

Biopsy of a cervical lymph node revealed metastatic adenocarcinoma. He was begun on 5-fluorouracil therapy and discharged, but suffered a progressive downhill course and ex-

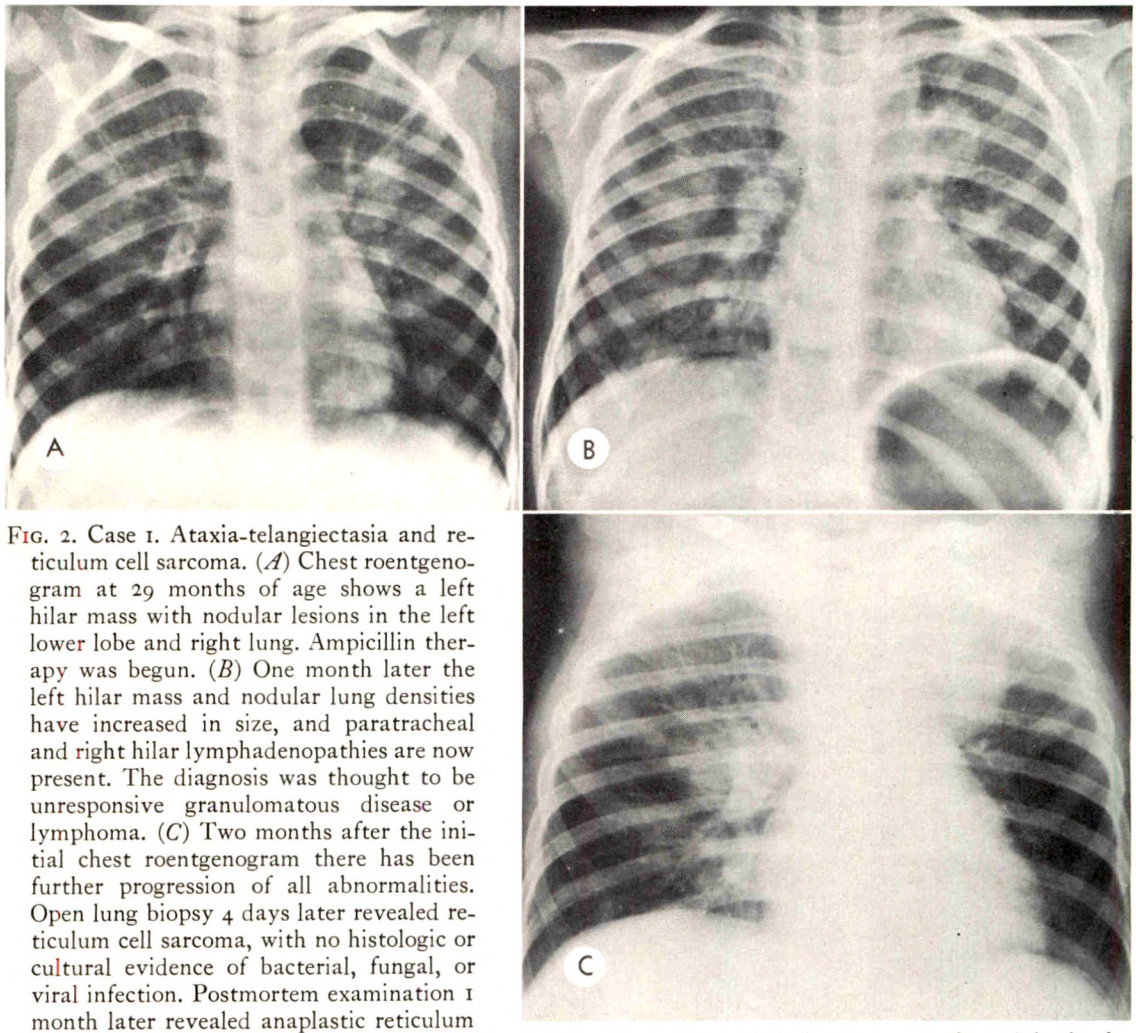

Fig. 2. Case 1. Ataxia-telangiectasia and reticulum cell sarcoma. (*A*) Chest roentgenogram at 29 months of age shows a left hilar mass with nodular lesions in the left lower lobe and right lung. Ampicillin therapy was begun. (*B*) One month later the left hilar mass and nodular lung densities have increased in size, and paratracheal and right hilar lymphadenopathies are now present. The diagnosis was thought to be unresponsive granulomatous disease or lymphoma. (*C*) Two months after the initial chest roentgenogram there has been further progression of all abnormalities. Open lung biopsy 4 days later revealed reticulum cell sarcoma, with no histologic or cultural evidence of bacterial, fungal, or viral infection. Postmortem examination 1 month later revealed anaplastic reticulum cell sarcoma involving lungs, hilar and mediastinal lymph nodes, with isolated metastatic nodules in the liver and right kidney.

pired 2 months later.

Autopsy disclosed a poorly differentiated infiltrating adenocarcinoma of the stomach with invasion of the transverse colon and retroperitoneal soft tissues and metastatic involvement of para-aortic, bronchopulmonary and cervical lymph nodes. The brain weighed only 600 gm. It contained a large porencephalic cyst which occupied the posterior two-thirds of the medial aspect of the left cerebral hemisphere and communicated with the left ventricle. The thymus weighed 2 gm. and had no identifiable Hassall's corpuscles. Lymph nodes, tonsils, spleen and intestinal Peyer's patches had markedly diminished to absent plasma cells and no germinal centers. The immediate cause of death was bilateral bronchopneumonia.

DISCUSSION

The roentgenologic features of most of the primary immunodeficiencies have been discussed elsewhere and will not be reviewed here.[2,10,15–17,20,22] In many instances early diagnosis of malignancy rests upon a high index of suspicion by the clinician and the radiologist.

Malignant neoplasms may be mistaken for inflammatory processes, as in Case 1 (Fig. 2, *A–C*), since infections occur so commonly in the immunodeficiencies. Enlarged lymph nodes due to hyperplasia may be difficult to differentiate from lymphoreticular and nonlymphoid metastatic ma-

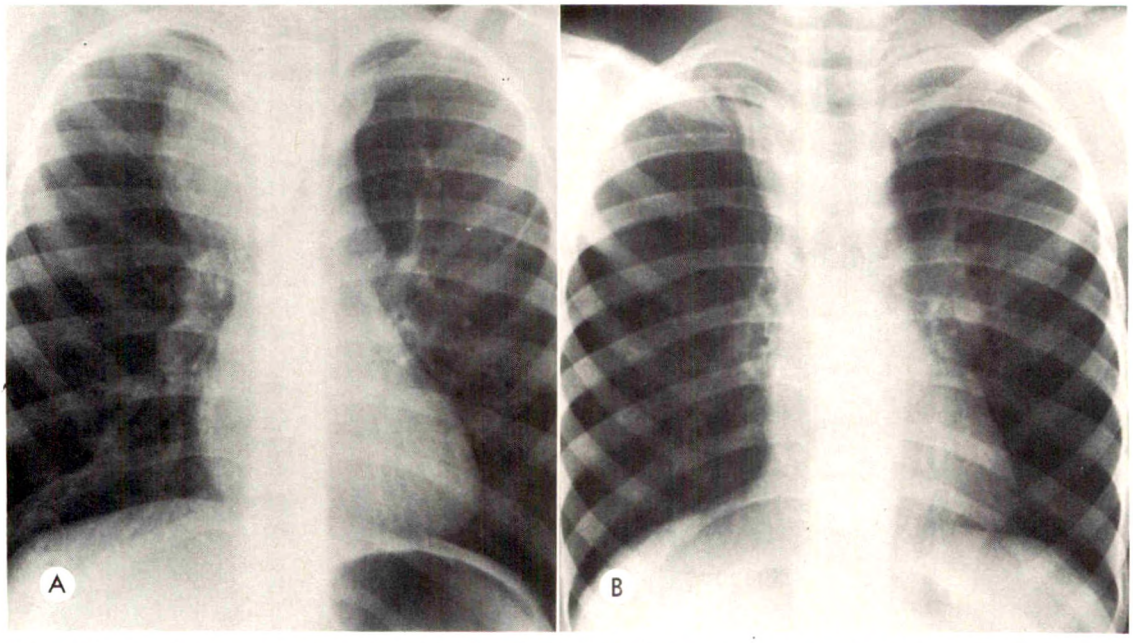

FIG. 3. Case II. Common variable immunodeficiency and Hodgkin's disease. (*A*) Chest roentgenogram at 11 years of age shows bilateral hilar lymphadenopathy and a large right superior mediastinal mass which deviates the trachea to the left. Focal chronic infiltrate in the right middle lobe is a residuum of previous inflammatory disease. Supraclavicular lymph node biopsy revealed Hodgkin's disease, mixed cellularity. (*B*) Four months later, following irradiation and chemotherapy. Right paratracheal and left hilar lymphadenopathy have recurred following earlier resolution. Radiation pneumonitis is present in the right upper lobe. The patient expired 3 months later with disseminated Hodgkin's disease.

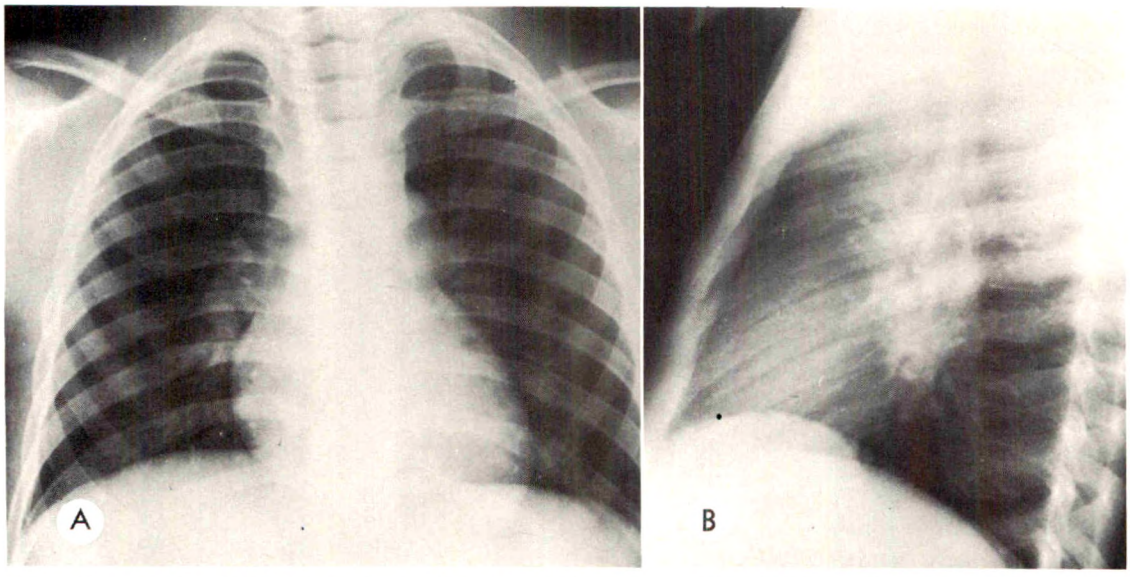

FIG. 4. Case III. Ataxia-telangiectasia and lymphocytic lymphoma. (*A* and *B*) Frontal and lateral chest roentgenograms at 7 years of age show bilateral hilar and superior mediastinal lymphadenopathy. Bone marrow examination and cervical lymph node biopsy revealed poorly differentiated lymphocytic lymphoma. The patient expired 14 months later with disseminated lymphoma.

lignancy. Gastrointestinal lymphoid hyperplasia occurs frequently in common variable immunodeficiency and may be clinically and roentgenographically impossible to differentiate from lymphoma (Fig. 5, *A–D*). In addition, the 2 conditions may coexist.

In this regard it is important to emphasize that only common variable immunodeficiency and the Wiskott-Aldrich syndrome are associated with benign reactive lymphoid hyperplasia. Therefore, hilar, mediastinal or other lymph node enlargement, or findings superficially resembling intestinal lymphoid hyperplasia in any of the other primary immunodeficiencies should be regarded as suspicious of malignancy (Fig. 2, *A–C*; and 4, *A* and *B*). Absent or low serum IgA is almost invariably found in immunodeficient patients with gastrointestinal lymphoid hyperplasia, but most individuals have other defects in humoral and/or cellular immunity.[1] The majority of these patients therefore have common variable immunodeficiency.

It is also re-emphasized that adenocarcinoma of the stomach occurs with a particularly high frequency in individuals with IgA deficiency, either isolated or in association with another primary immunodeficiency disease.[5] Knowledge of this association might have led to a correct preoperative diagnosis in Case IV, although the outcome would not have been altered.

The estimated risks of malignancy in the immunodeficiency syndromes are listed in Table 1. These risks, while not high in relation to the population at large, are exceedingly high in relation to an age-matched population,[14] since with the exception of common variable immunodeficiency and selective IgA deficiency, most of the reported malignancies have occurred during the first 2 decades of life.[13]

An extensive discussion of the pathogenetic mechanisms involving oncogenesis in the primary immunodeficiencies is beyond the scope of this paper. The broad category of abnormal immunologic surveillance, that is, deficiency in homeostatic defense mechanisms that protect the normal individual from neoplastic change, has been suggested.[23] If this were the major factor in oncogenesis, however, one would expect the relative frequencies of the various tumors in the immunodeficiencies to be similar to the general population.[14] The predominance of lymphoreticular malignancies suggests intrinsic abnormalities of the lymphoid system resulting in greater than normal malignant transformation of lymphoid cells.[14] The relationships are complex and have not been fully resolved.

SUMMARY

The incidence of malignant tumors in the primary immunodeficiency diseases is dramatically increased. Four patients with primary immunodeficiencies who developed fatal malignancies are reported.

Lymphoreticular tumors and leukemia predominate in most conditions, but epithelial neoplasms are the most common tumors in selective IgA deficiency, and they comprise over one-fourth of malignancies in common variable immunodeficiency. With the exception of common variable immunodeficiency and the Wiskott-Aldrich syndrome, hyperplasia of lymphoid tissue usually does not occur. Lymph node enlargement in any of the other immunodeficiencies is therefore most likely secondary to malignancy. Benign gastrointestinal nodular lymphoid hyperplasia occurs frequently in common variable immunodeficiency and in some instances may be impossible to differentiate roentgenologically from lymphoma.

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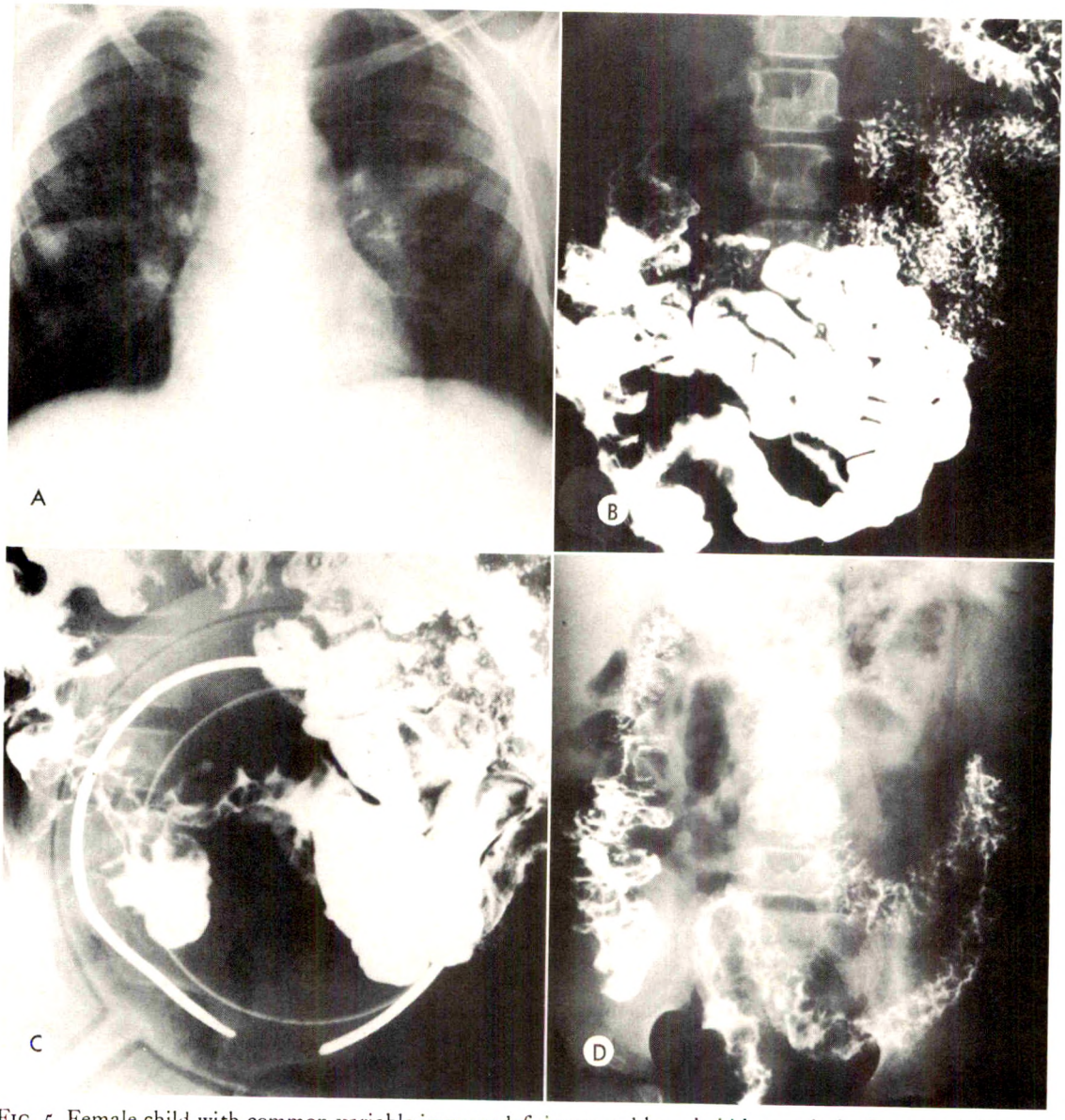

FIG. 5. Female child with common variable immunodeficiency and lymphoid hyperplasia. Immunodeficiency and lymphoid hyperplasia. Immunoglobulins: IgA absent, IgG decreased, IgM increased. Recurrent viral and bacterial infections with generalized peripheral lymphadenopathy. (*A*) Chest roentgenogram at 8 years of age shows bilateral hilar and right paratracheal lymphadenopathy and bilateral pulmonary infiltrates. (*B*) Upper gastrointestinal and small bowel series at 10 years of age at a time when a right lower quadrant mass was palpated. Extensive nodular impressions indent the terminal ileum and cecum, and enlarged mesenteric lymph nodes separate loops of distal small intestine. The mucosa of the stomach and proximal jejunum is also nodular. (*C*) Compression spot roentgenogram of terminal ileum. The appearance is indistinguishable from lymphoma. (*D*) Evacuation roentgenogram of a barium enema examination at 10 years of age. Nodular lymphoid hyperplasia involves the entire colon. An enlarged spleen displaces the splenic flexure inferiorly.

Biopsy of an enlarged axillary lymph node at 11 years of age revealed hyperplasia. On clinical follow-up the right lower quadrant abdominal mass waxed and waned coincident with intercurrent infections. Two years after the gastrointestinal roentgenograms there was no clinical evidence of lymphoma.

We also thank Colonel Edgar O. Ledbetter, MC, USAF, for providing clinical information on the patient with common variable immunodeficiency who is featured in Figure 5.

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IRRADIATION OF STAGE I AND II HODGKIN'S DISEASE*

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DISAGREEMENT continues over the extent and dose of irradiation needed to control Stage I and II Hodgkin's disease. Reports of the potential benefit using wide-field irradiation appeared as early as 1931[8] with definite improvement in survivals attributable to extended-field therapy published by Peters in 1950.[22] However, the concept of routine wide-field irradiation did not become generally accepted until the 1960s following the improved survivals reported at Stanford[14] and subsequently confirmed at other centers.[10,23]

Although the interim report of the National Hodgkin's Study Committee[20] indicated no significant difference in survivals as a function of irradiation extent, most centers have adopted an aggressive radiotherapy approach. However, several important questions remain partly or entirely unanswered.

What time-dose regimen results in optimal local control-rates with minimum morbidity?

What role does the histologic subtype play in the over-all survival? How should the treatment approach be altered by the histologic subtype?

Should the apparent site of origin affect management policy?

This retrospective analysis was undertaken to document the results of varying doses and treatment volumes on the survival, complication, local recurrence and extension rates of 147 patients with Stage I and II Hodgkin's disease. The role of the primary site and histologic subtype was examined. One-hundred and eleven additional patients seen by the Radiation Therapy Service with Stage III and IV disease were not included in this report so that the authors could analyze a group of cases receiving irradiation as their sole modality of initial treatment.

MATERIAL AND METHOD

From 1960 to 1970, 147 previously untreated patients with Stage I or II Hodgkin's disease were seen by the Radiation Therapy Service of Walter Reed General Hospital. All patients had bipedal lymphograms and 36 underwent staging laparotomies prior to treatment. The evaluations included the usual laboratory, radiographic, and biopsy examinations recommended by Rosenberg and Kaplan.[24] In every instance, the diagnosis was initially confirmed by the Walter Reed General Hospital Department of Pathology. The original biopsy material was reviewed, when necessary, to conform with the Rye histopathologic classification of Hodgkin's disease.[16] The cellular phase of nodular sclerosis was not categorized as a separate entity. Eight of the 147 cases had unequivocal evidence of Hodgkin's disease, but could not be categorized because of inadequacy of material and were designated "unclassified."

Over the period 1960 to 1970, treatment policies underwent considerable transition. As a result, 3 distinct treatment groups emerged reflecting these changing irradiation approaches. Sixty-four of the 147 cases were irradiated to clinically involved lymph node regions, regardless of histo-

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logic subtype, occasionally including 1 adjacent nodal region but without an attempt to treat all adjacent areas. These cases, referred to as treatment Group "A," include 19 cases randomly assigned within the National Hodgkin's Disease Study. Most of the remainder were treated between 1960 and 1965.

An additional 53 cases received extended-field therapy to include adjacent areas clinically or radiographically free of disease, again regardless of the histologic subtype. The portals included an upper extended-field (mantle), but without systematic irradiation of the paraaortic lymph node chains. The treatment consisted of less than total central lymphatic (total nodal) irradiation in all patients, but did include paraaortic irradiation in 8 cases, 7 of whom bore the mixed cellularity subtype and 1 who manifested systemic symptoms. These 53 cases are referred to as Group "B", and include 23 cases randomly assigned as part of the national Hodgkin's Disease Study.

The "C" group consists of 30 Stage I–II cases irradiated in the 1960–1970 period, but conforming to the following treatment policy adopted in 1971, taking both stage and histologic subtype into consideration:

All Stage IB, IIB and all mixed cell types received total central lymphatic (total nodal) irradiation, with a minimum tumor dose of 3,600 rads in 4–6 weeks. Stage IA and IIA nodular sclerosing and lymphocytic predominance cases received 3,600 rads minimum tumor dose to an upper extended-field (mantle) and to the paraaortic lymph nodes.

Although the splenic area was not irradiated routinely, a small "dogleg" was occasionally added in the left upper quadrant to cover the resected splenic hilus.

Between 1967 and 1969 a group of patients received tumor doses in excess of 4,000 rads and several received tumor doses of 4,400 rads in 4 weeks. The latter doses were largely related to a dosimetry miscalculation. Supervoltage equipment (2 MeV or cobalt 60) was utilized in the treatment of every patient at distances of 80–100 cm. Lead lung shields were constructed according to the specific disease distribution of each patient, shielding as much lung as feasible for the individual disease distribution.

Follow-up information on each case included data on the time and location of disease recurrence or type of extension and date of death with causes. Data were available for 96 per cent of all patients, with most followed directly at Walter Reed Hospital or through its tumor registry. Autopsy reports, when available, were utilized to document the cause of death.

Survival data for the 3 groups, with and without progression of disease (extension or recurrence) following initial irradiation, are evaluated by the life table method of Cutler and Ederer.[3]

RESULTS

Of the 147 patients in this series 78 per cent (115) are male and 94 per cent (138) Caucasian. The patients ranged in age from 12 to 79 years with the median age of 24. This predominance of young males obviously reflects the military population which Walter Reed Hospital serves.

STAGE

All cases were staged using both the Rye and Ann Arbor staging system to allow comparison of this series with previously published and future series of Hodgkin's disease.

Using the Rye staging system 39 per cent (58/147) of the cases were staged as $I_{1-2}A$, 5 per cent (6/147) as IB, 43 per cent (63,147) as IIA, and 14 per cent (20/147) as IIB. Under the Ann Arbor system[2] 35 per cent are Stage I, 65 per cent, Stage II. No extralymphatic (E) primary lesions were encountered in these 147 cases, nor did any present in Waldeyer's ring or Peyer's patches.

ANATOMIC DISTRIBUTION

The anatomic distribution of disease at

TABLE I

DISEASE PREVALENCE BY HISTOPATHOLOGIC SUBTYPE

Distribution of Lymphadenopathy	Lymphocytic Predominance	Nodular Sclerosis	Mixed Cellularity	Unclassified	Totals
Cervical	15	31	39	3	88
Supraclavicular	1	24	21	5	51
Axillary	6	18	25	1	50
Mediastinal	2	45	28	6	81
Pelvic	1	0	0	0	1
Inguinal	1	1	0	0	2
Total Patients	19	64	56	8	

time of diagnosis was similar to other large published series. However, several interesting differences were noted. The majority of patients had cervical and/or mediastinal involvement and about one-third manifested supraclavicular and/or axillary lymphadenopathy at the time of diagnosis (Table 1). The more aggressive histologic subtype (mixed cellularity) had a similar pattern of distribution for these Stage I–II patients. The inguinal area was infrequently involved with all histologic subtypes. Surprisingly, no case of an extranodal primary lesion was present; however, the authors did not attempt to separate large mediastinal masses from actual lung involvement.

Patients with nodular sclerosing subtype demonstrated a 70 per cent (45/64) occurrence of mediastinal involvement, identical to that reported by Dorman.[4]

Analysis of the location of disease as a function of histologic subtype reveals a high incidence of lymphocytic predominance in patients presenting with mid-to-high cervical lymphadenopathy as the only demonstrable disease. Of 19 lymphocytic predominant cases, 8 presented in mid-to-high cervical chains. These 8 cases account for two-thirds of all high cervical presentations in this series and for 42 per cent of all the lymphocytic predominance cases. Two additional lymphocytic predominance cases presented as solitary axillary lymphadenopathy and 2 within inguinal or pelvic lymph nodes. In addition, 2 cases of mediastinal lymphadenopathy are noted—an unusual finding.[4]

The "excess" (70 per cent) occurrence of mediastinal involvement with nodular sclerosing has been noted. Mediastinal involvement was also common in mixed cell type, occurring in 50 per cent of such cases.

Of the 11 patients presenting with mediastinal involvement only (Stage 1), 7 were nodular sclerosing, 3 mixed cell, and 1 unclassified. Four contiguous extensions to lung from mediastinal lymph nodes later occurred with patients bearing nodular sclerosing disease.

HISTOLOGY

The occurrence of histologic subtype by Rye Classification is outlined in Table II; it is similar to other published series.[7,15] As expected, nodular sclerosing, the most frequent type, accounted for 43.5 per cent. The absence of any patient wlth lymphocyte-depleted type probably reflects the exclusion of Stage III disease and the bias

TABLE II

DISTRIBUTION OF HISTOPATHOLOGIC SUBTYPES

Subtype	Number	Per Cent
Lymphocytic predominance	19/147	12.9
Nodular sclerosing	64/147	43.5
Mixed cellularity	56/147	38.1
Lymphocytic depleted	0	—
Unclassified	8/147	5.5

of the young male population. Patients with lymphocyte-depleted subtype tend to be older and present in an advanced stage.[19,25]

IRRADIATION GROUPS

The characteristics of the 3 retrospective irradiation groups were analyzed to assure that the make-up of the groups was reasonably comparable. The percentages of age range, sex, Rye and Ann Arbor stages and histopathologic subtypes are compared in Tables III through V. The percentages are shown for each category with the absolute number in parentheses. Although the "A" group is weighed in favor of earlier Rye-stage patients compared to the 2 other categories (53 per cent *versus* 28–30 per cent), the "C" group is favorably biased with an excess of nodular sclerosing histologies (66.7 per cent *versus* 34.4 per cent in "A" group). As expected, a larger percentage of patients in the "C" group underwent staging laparotomy (18/30), compared to the "A" group (10/64) and "B" group cases (8/53). Although this fact pre-

TABLE III

AGE-SEX COMPARISON BY TREATMENT GROUP

Age Group (years)	Under 15	16–20	21–25	26–30	31–35	36 or over	Totals	Male	Female
Treatment Group "A"	1.6 (1)*	17.2 (11)	42.2 (27)	14.0 (9)	9.4 (6)	15.6 (10)	64	73.4 (47)	26.6 (17)
Treatment Group "B"	3.7 (2)	13.3 (7)	50.9 (27)	15.1 (8)	7.6 (4)	9.4 (5)	53	81.1 (43)	18.9 (10)
Treatment Group "C"	0 (0)	20.0 (6)	53.4 (16)	13.3 (4)	3.3 (1)	10.0 (3)	30	83.3 (25)	16.7 (5)

* Percentages are shown with absolute number in parentheses.

TABLE IV

STAGE ANALYSIS BY TREATMENT GROUP

Initial Stage

	Rye				Ann Arbor	
	$I_{1-2}A$	$I_{1-2}B$	IIA	IIB	I	II
Treatment Group "A"	53.1 (34)*	7.8 (5)	32.8 (21)	6.3 (4)	52 (33)	48 (31)
Treatment Group "B"	28.3 (15)	1.9 (1)	49.1 (26)	20.7 (11)	21 (11)	79 (42)
Treatment Group "C"	30.0 (9)	0	53.3 (16)	16.7 (5)	23 (7)	77 (23)

* Percentages are shown with absolute numbers in parentheses.

TABLE V

ANALYSIS OF HISTOPATHOLOGIC SUBTYPE BY TREATMENT GROUP

	Histopathologic Subtype (Rye)				
	Lymphocytic Predominance	Nodular Sclerosis	Mixed Cellularity	Lymphocytic Depleted	Unclassified
Treatment Group "A"	15.6 (10)*	34.4 (22)	37.5 (24)	0	12.5 (8)
Treatment Group "B"	13.2 (7)	41.5 (22)	45.3 (24)	0	0
Treatment Group "C"	6.7 (2)	66.7 (20)	26.6 (8)	0	0
	(19)	(64)	(56)	0	(8)

* Percentages are shown with absolute numbers in parentheses.

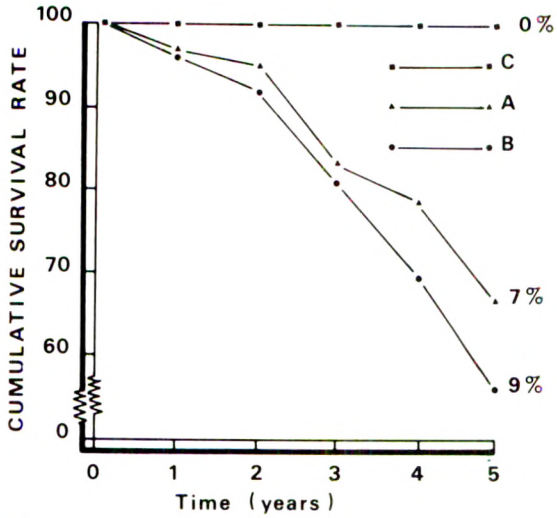

FIG. 1. Life table survival of the 3 irradiation groups living with or without evidence of active Hodgkin's disease.

"A"—Irradiated to clinically enlarged lymph nodes, occasionally including one adjacent lymph node region prophylactically.

"B"—Mantle or mantle plus paraaortic irradiation but *not* conforming to current policy "C."

"C"—Extent of irradiation according to Stage and histology as follows: all Rye IB or IIB and all mixed cellularity received total lymph node irradiation; all Rye IA or IIA lymphocytic predominant or nodular sclerosing received mantle plus paraaortic irradiation sparing pelvic and inguinal areas.

sents a bias in favor of the "C" group, it alone does not explain the marked differences in survival obtained within the 3 treatment categories.

Tumor doses were expressed in a single number, the nominal standard dose in rets using the Ellis formula*[5] to compare complications (myelitis, symptomatic pneumonitis, or pericarditis), within 3 dosage ranges. These data, plotted in log-log curve in Figure 3, show a straight-line relationship between per cent complications and increasing dose of irradiation. Local recurrence (excluding marginal misses and tumor extensions) did not conform to a similar log-log plot, suggesting that total tumor dose, not elapsed time, is the primary determinant of local tumor control. Six of seven local recurrences occurred at or below doses of 3,600 rads.

* Tumor dose = N.S.D. × (number fractions)$^{-.24}$ × (elapsed time)$^{-.11}$.

NEW MANIFESTATION OF DISEASE

The first new manifestation of disease was compared among the 3 irradiation groups (Table VI). Nearly half (30/64) of the patients within the "A" group developed recrudescence of Hodgkin's disease. Twenty-two of these 30 first new manifestations or 73.5 per cent were within lymph nodes. Only 16 of 53 cases (30 per cent) within the "B" category showed any new manifestation of the disease and 44 per cent (7/16) were within lymph nodes. Nodal extensions were eliminated within the "C" group.

SURVIVAL

Survival time patterns, using the life table method, were plotted for the 3 irradiation categories. Over-all as well as extension-free (NED)† survivals were determined (Fig. 1; and 2). The standard errors at the end of the fifth year are noted. The standard T-test was applied to all com-

† NED= no evidence of disease.

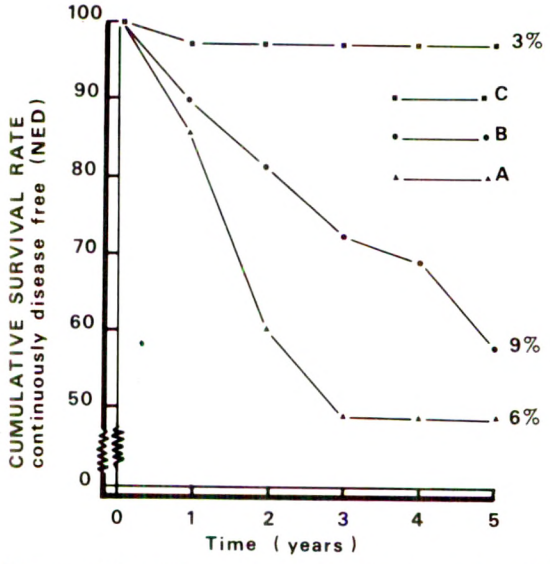

FIG. 2. Life table survival of patients continually disease free (NED) measured from completion of initial irradiation.

binations of the 3 treatment groups for both survival graphs. All differences were found to be highly significant ($p \leq .01$).

The curves demonstrate a marked improvement in extension-free survival using the "C" or current policy of irradiation contrasted to the less extensively irradiated groups.

Several additional factors affecting survival were noted as follows:

Only 1 of 11 patients with mediastinal primary lesion died of disease (91 per cent survival), yet 2 patients died of radiation pneumonitis, lowering the absolute survival to 73 per cent (8/11).

Ten of the 12 patients with high cervical presentations received local irradiation only with an absolute survival for the entire group of 92 per cent (11/12). The 75 per cent absolute survival, free of disease, of the 8 lymphocytic predominant high cervical cases is identical to the 77 per cent NED survival of the entire patient population with lymphocyte predominant Hodgkin's disease.

TABLE VI

FIRST NEW MANIFESTATION OF HODGKIN'S DISEASE BY TREATMENT GROUP

	"A"	"B"	"C"
Number of Patients Treated	64	53	30
Local Recurrence	4	2	1
Lymph Node Extension	22	7	0
Organ Extension	4	7	0
Totals	30	16	1

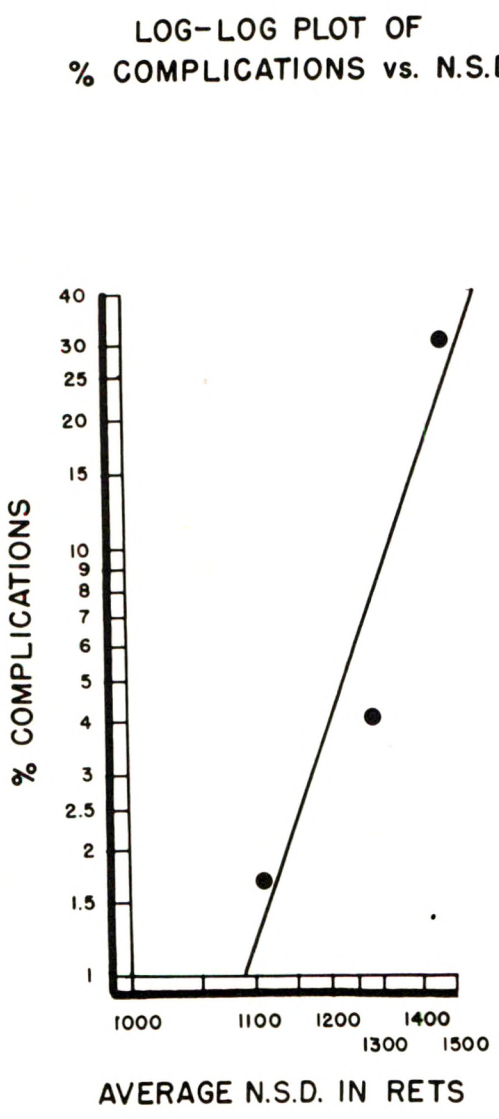

FIG. 3. Per cent symptomatic complications ("pneumonitis," "myelitis," or "pericarditis") as a function of average dose in rets using Ellis formula.

DISCUSSION

Since the patients seen with Hodgkin's disease at Walter Reed General Hospital represent a somewhat unique population comprised largely of young males, some caution must be exercised in comparing this analysis with other published series.

Only 9 patients or 6 per cent in this series of 147 cases were Black. The apparent resistance of the Black race to leukemia, lymphomas, and Hodgkin's disease has been noted by MacMahon.[17,18] This 6 per cent occurrence in our series represents less than the expected number, if the incidence were equal among Black and white racial populations. The reason for this decreased frequency is unknown and bears further investigation.

Females have a somewhat greater occurrence of nodular sclerosing Hodgkin's disease. In the Stanford material,[4] this occurrence is 85 per cent of all initial biopsies

compared to 67 per cent seen in males. The association of nodular sclerosis with early-stage mediastinal involvement does not explain the improved survival in females, since Tubiana *et al.*[25] were not able to demonstrate an association between survival and mediastinal involvement. The predilection for mediastinal disease is equal among male and female patients bearing the nodular sclerosing subtype.[4]

Analysis of the anatomic distribution of disease at time of diagnosis reveals several significant findings. The 70 per cent occurrence of mediastinal involvement is especially surprising in view of the small number (22 per cent) of females in this series. The increased frequency of mediastinal presentations is well recognized in association with the nodular sclerosing subtype.[4]

Inguinal and pelvic presentations were quite infrequent, accounting for only 3 of 147 cases. The relative paucity of inguinal presentations in Hodgkin's disease contrasted to the lymphomas has been noted by others.[12] Inclusion of only early cases (Stage I–II) has naturally excluded the more advanced cases in whom inguinal lymph node involvement is more frequent.

The association between high cervical nodal presentations and lymphocytic predominance was an unexpected finding. Peters and Middlemiss[21] have previously noted the favorable prognosis of solitary peripheral sites of the lymphocytic predominant subtype. Similarly, finding this histology in 67 per cent (8/12 cases) of all high cervical lymph node presentations suggests that this same association may account for the excellent prognosis noted.[7,9] These high neck presentations accounted for 8/19 (42 per cent) of all lymphocytic predominance cases. Moreover, the prognosis of these patients did not differ significantly from the entire lymphocytic predominant-bearing group. Two cases of the lymphocytic predominance subtype involving the mediastinum are noted—a rare association.[4]

This series reveals a definite association (Table I) between axillary presentations and mixed cell histologic subtype. One-half of the axillary tumors were of the mixed cell type. Conversely, 45 per cent (25/56) of patients with the mixed cell pattern had initial axillary involvement compared to 31 per cent (6/19) for lymphocytic predominance and 28 per cent (18/64) of nodular sclerosis. This greater frequency of axillary involvement in conjunction with the mixed cellularity subtype at least partially explains the poorer prognosis associated with axillary presentations.[7]

Analysis of the site of first new manifestation of disease as a function of irradiation group shown in Table VI reveals an inverse relationship between the extent of irradiation and the percentage of nodal extensions. Nearly three-fourths of all first new manifestations of disease in the "A" group were nodal extensions compared to 44 per cent of the 16 extensions in the "B" group. No nodal extensions were seen in the 30 "C" group.

All new manifestations of Hodgkin's disease declined sharply with increasing extent of irradiation. Nearly 50 per cent of all patients within the "A" group returned with further disease compared to 30 per cent of the "B" cases and 3.3 per cent of the "C" patients. Twenty-two patients within the "A" group and 7 within the "B" category developed lymph node extensions as their sole first new manifestation of disease. These 29 cases account for 62 per cent of all first new manifestations. Many of these 29 extensions would have been prevented by more extensive initial irradiation. Obviously, extended-field irradiation would not have affected the outcome in the 11 patients presenting with organ involvement as their first new manifestation of disease.

Examination of the survival data (Fig. 1; and 2) demonstrates a clear superiority of the "C" group over the "A" and "B" policies. Comparing the 5 year extension-free survivals for the 3 irradiation categories, the figure falls to 49 per cent for the "A" cases, 58 per cent for "B" patients, while remaining at the 95 per cent level for the "C" group. These differences

are highly significant with a p value $\leq .01$. This finding demonstrates the danger of assuming that prognosis is unaltered by recrudescence of disease activity. Those cases allowed to extend to contiguous or distant lymph nodes almost invariably develop organ involvement and, despite retreatment with chemotherapy or irradiation, die of disease. The relapse-free interval has also been reported by Kaplan[13] to be an important prognosticator. Sixty-five per cent of our cases showing extensions have died of disease with only 2 patients alive NED for 2 years or greater following retreatment. An additional 16 patients are alive with active Hodgkin's disease. The assumption that local irradiation of involved sites produces the same survival as initial extended-field therapy is clearly invalid.

Another common assumption not confirmed by this analysis is that a dose of 4,400 rads delivered in 4 weeks is required for control of Hodgkin's disease. Six recurrences occurred at or below a total tumor dose of 3,600 rads with only 1 noted between 3,600 and 4,000 rads. The 4.7 per cent local recurrence rate is not significantly different from that reported at considerably higher dose levels.[15] This incidence is reduced to 2.7 per cent (7/260) when considering the recurrence rate in tumor-bearing areas. Excellent tumor control rates have also been reported by Johnson *et al.*,[11] using the relatively lower dosage regimens of 3,600 to 4,000 rads in 4 to 8 weeks. The rate of tumor control seems to be independent of the total time of the treatment course as long as the elapsed time does not exceed 8 weeks.[6]

However, the rate of complications increases logarithmically as the tumor dose rises above 4,000 rads, especially when the treatment course is limited to 4 weeks. The rate of symptomatic pneumonitis, pericarditis, and myelitis (not including Lehrmitte's syndrome) obeys a log-log plot, showing a geometric increase of complications with increasing dose (Fig. 3). The complication rate at doses of 4,000 rads or below, given in 20 treatments over 29 days (NSD = 1,340 rets), is an acceptable maximum of 10 per cent. However, a 10 per cent increase in dose from 4,000 to 4,400 rads delivered in the same 29 days (NSD = 1,485 rets) doubles the risk of morbidity. Although the latter 20 per cent complication rate can be partly averted using lung, spinal cord, and heart shielding techniques utilizing varying thicknesses of lead, significant morbidity persists at the 4,400 rad level.[12] A 32 per cent incidence of severe damage was observed in 38 cases receiving an average of 1,475 rets in this series. Four patients died as a direct result of the pulmonary damage, which occurred at doses in excess of 4,000 rads.

In contrast, at doses averaging 1,290 rets (3,800 rads, 20 fractions, 29 days), the morbidity falls to a low 4 per cent (2/48). Only 1 local recurrence was seen within this 3,600–4,000 rad dose range.

CONCLUSION

One must conclude on the basis of the above analysis that tumor doses in excess of 3,600 or 4,000 rads add only to morbidity, and not to local control.

Secondly, the technique of irradiating involved lymph node groups only, leaving other areas to be treated "later," apparently denies the possibility of cure to a significant number of patients with early stage Hodgkin's disease. Recurrence or extension almost uniformly leads to eventual death from disease despite retreatment.

No case of second primary cancer has been documented in the patient population included in this report. However, the number at risk is relatively small and chemotherapy was reserved only for generalized recurrence. Since the reported 20 times expected incidence occurred with the combination of total-nodal and multiple-agent chemotherapy,[1] one would not expect an increased incidence of second primary lesions in this series.

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IODINE 125 SOURCE IN INTERSTITIAL TUMOR THERAPY*

CLINICAL AND BIOLOGIC CONSIDERATIONS

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INTERSTITIAL cancer therapy is the treatment of a malignant tumor by radiation from encapsulated radioactive sources placed within the tumor. For the past 60 years, several encapsulated radionuclides have been used at Memorial Hospital, New York City for interstitial cancer therapy. Radon 222 was used initially, but since the advent of nuclear reactors, gold 198 and iridium 192 were used; all these radionuclides have a high energy gamma radiation.

In 1965, iodine 125 sources, a low energy gamma-ray emitting radionuclide, was introduced as a substitute for radon 222 or gold 198 sources. One of the chief advantages in using iodine 125 was the reduction in exposure to personnel, patients and their families. In Table 1, a few selected physical parameters are given of commonly available radionuclides for interstitial therapy, including iodine 125.

We have previously presented clinical experience with iodine 125 seed implants in prostatic carcinoma and in apical carcinoma of the lung elsewhere.[6,7]

This paper presents additional clinical data for 2 groups of patients. This information was used to estimate the biologic effects on normal and neoplastic tissues of widely differing energies and dose rates of encapsulated gamma-emitting radionuclides.

The 2 groups of patients studied were:

1. Those with metastatic carcinoma in neck lymph nodes implanted with iodine 125, radon 222 or iridium 192 encapsulated sources; and
2. Those with primary lung tumors found unresectable at thoracotomy, which were implanted either with radon 222 or iodine 125 seeds.

TABLE I

PHYSICAL PROPERTIES OF RADIONUCLIDES USED AS SEEDS FOR IMPLANTATION

Radionuclides	T 1/2 (days)	Γ (r/mc-hr. at 1 cm.)	HVL (cm. Pb)
Radon 222	3.8	8.25	1.4
Iridium 192	75	5.5	0.24
Iodine 125	60	1.4	<0.001

MATERIAL AND METHOD

CLINICAL DATA

The first group consists of 98 patients with metastatic neck lymph nodes implanted with iodine 125, radon 222 or iridium 192 encapsulated sources during the period of 1965 to 1972. Most of these patients received external irradiation, usually 4,000 rads in 4 weeks, prior to interstitial implantation. The majority of the metastatic neck lymph nodes were from head and neck primary lesions with the histology of epidermoid carcinomas.

The second group consists of 105 patients with primary unresectable lung carcinoma, implanted either with radon 222 or iodine 125 seeds during the period 1963 to 1971. The majority of these patients were treated with interstitial implantation only. Supplementary external irradiation of 4,000 rads in 4 weeks was given to 8 patients because of a poor geometric pattern of the seed distribution (postoperative irradiation), and to 5 patients because the primary tumor was too large before the

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exploratory thoracotomy (preoperative irradiation). Most of the patients had a Stage III cancer of the lung, as defined by the American Joint Committee for Staging and End Results.

IMPLANTATION PROCEDURE

The implantation technique consists of 3 steps:

First, unloaded stainless steel, 16 gauge needles are inserted into the tumor, spaced 1 cm. apart. The entire tumor volume is implanted allowing for a 1 cm. peripheral margin.

The second step involves the calculation of the radioactivity required for each implant. This is done by the "dimension averaging" system, in use at Memorial Hospital for the past 15 years. The details of the method, as well as the mathematical analysis of this system were published elsewhere.[5] Briefly stated, the 2 dimensions can be measured directly with a ruler, while the third dimension is estimated by the length of the inserted needles. After averaging the 3 dimensions, the required activity is obtained by the use of the following formula: Required Activity (mc) = Average Dimension (cm.) $\times K$, where K is an empirical factor, specific for a given radionuclide. The K for radon 222, iodine 125 and iridium 192 is 10, 5, and 5, respectively. To find the number of sources needed, the millicurie value is divided by the average activity of sources in stock.

The third step is to insert the radioactive seeds. Several seeds are introduced through each needle, using the seed inserter, spaced no less than 0.5 cm. and no more than 1.5 cm. apart, as each needle is withdrawn.

DOSAGE CALCULATION

After the seed localization by means of orthogonal and stereoradiographs, the 3 dimensional isodose distribution within an implant is generated by the computerized systems of dosimetry developed at Memorial Hospital.[10] A representative dose distribution from equivalent spatial distribution for iodine 125 and radon 222 is shown in Figure 1.

RESULTS

A. INTERSTITIAL IMPLANTS OF THE METASTATIC NECK LYMPH NODES

Table II shows the over-all results of the local tumor control rate and of the complication rate in patients treated with iodine 125, radon 222 or iridium 192. The local tumor control rates with iodine 125, radon 222 and iridium 192 were 78 per cent (38/49), 65 per cent (15/23) and 58 per cent (7/12), while the local complication rates were 17 per cent, 35 per cent and 43 per cent, respectively. The local tumor control was defined as complete tumor regression with no subsequent local recurrence. The early local complications were mostly moist desquamation and occasionally ulcer and abscesses, usually developing in the first 3 months after implantation. The late complications included fibrosis, fistulae, ulcers and skin necrosis.

The average regression rate of the implanted tumors is shown in Figure 2. It is interesting to note that most of the tumors implanted with iodine 125 seeds reached the clinical nonpalpable level in a period corresponding to the one-half life of iodine 125 (*i.e.*, 60 days). The variation of the regression rate was more pronounced in the iodine group as compared to the radon group.

Table III shows the local tumor control rate as a function of the implanted minimum tumor dose. It can be shown that the iodine 125 implants with a delivery of the minimal effective tumor dose of 16,000 rads have a higher therapeutic ratio than either radon 222 or iridium 192. The difference in the complication rate between the iodine group and the radon group was statistically significant ($p < 0.05$), while the local control rates were equally high in both groups. The equivalent single dose (ESD), computed according to Worthley,[11] shows that the ESD of 5,300 to 5,600 rads is required to control more than 80 per cent of the implanted tumor, although the

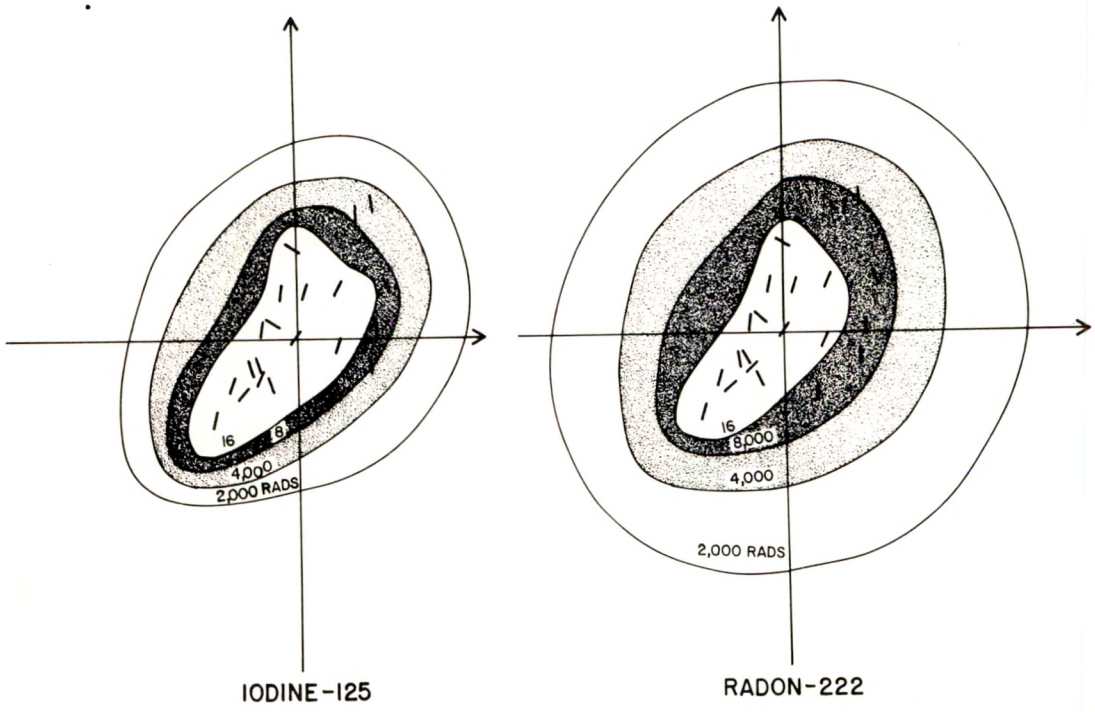

FIG. 1. Comparative dose distributions in tissue from equivalent spatial distribution for iodine 125 and radon 222. Implanted area: right neck, 20 seeds anteroposterior projection. Normalization: equal dose at 1 cm. per millicurie destroyed.

complication rates differ widely (16 per cent to 46 per cent).

B. INTERSTITIAL IMPLANTS OF UNRESECTABLE CARCINOMA OF THE LUNG

The local tumor control and complication rate as well as the over-all average survival time is shown in Table IV for patients whose tumors were implanted either with radon 222 or iodine 125 seeds. The local tumor control rates with iodine and radon seeds were 67 per cent and 45 per cent respectively. This difference was statistically significant at the level of $p=0.05$. No significant difference in the complication rates was noted. The complications associated with the implants were: empyema; septicemia; pulmonary hemorrhage; and esophagitis when the implanted volume was proximal to the

TABLE II

INTERSTITIAL IMPLANT THERAPY FOR METASTATIC CARCINOMA IN NECK LYMPH NODES

	Iodine 125	Radon 222	Iridium 192
1. Total number of patients	58	26	14
2. Average survival in months from the time of implantation	11 (2–30)*	9 (3–23)	13 (3–44)
3. Number of patients who survived less than 4 months	9	3	2
4. Local tumor control rate in patients surviving 4 months or more	38/49=78%	15/23=65%	7/12=58%
5. Complication rate	10/58=17%	9/26=35%	6/14=43%

* Figures in the parentheses denote the ranges of survival time.

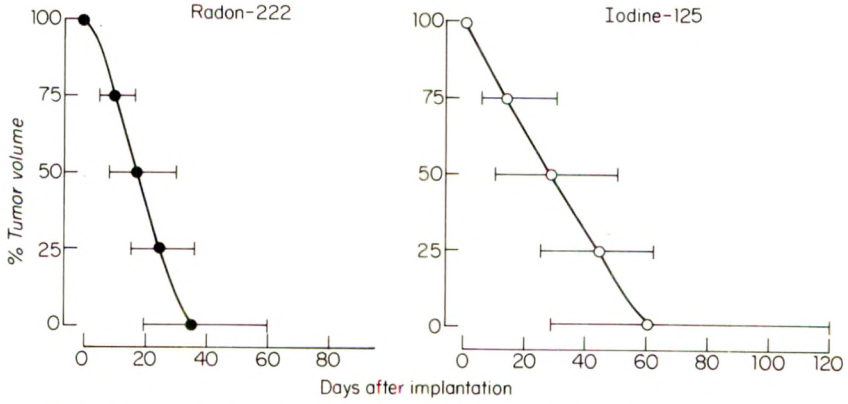

FIG. 2. The rate of the implanted tumor regression as a function of days. The horizontal bar denotes the ranges of the days.

esophagus. The average tumor volume was larger in the pulmonary group than in the neck lymph node groups.

The cumulative survival for this group of patients is shown in Figure 3, calculated by the Berkson-Gage method. The 5 year cumulative survival with iodine 125 implants is 12.5 per cent and with radon 222 implants, 4 per cent. It is interesting to note that the local tumor control rate after a delivery of the minimal effective tumor dose of 16,000 rads from iodine 125 sources in this group of patients is comparable with that obtained from the previous Group I patients (Table v).

DISCUSSION

There are distinct physical advantages of iodine 125 sources as a radon 222 or gold 198 substitute for interstitial implantation of malignant tumors. Shielding for iodine 125 seeds is easily constructed and lightweight, mainly because of low energy gamma radiation. No external hazards to other patients or personnel exist, since the radiation within the implanted tumors rapidly attenuates. Furthermore, the use of the manual afterloading of the seeds drastically reduces the radiation exposure to the medical and paramedical personnel. Other advantages of the iodine 125 include

TABLE III

TUMOR CONTROL RATE AS A FUNCTION OF TUMOR DOSE

(Metastatic Neck Lymph Nodes)

Radioactive Seeds	Minimum Tumor Dose (rad)	ESD (rad)	Tumor Control (Per Cent)	Complication (Per Cent)
Iodine 125	4,000	1,325	2/2 (100)	0/2 (0)
	8,000	2,650	9/14 (64)	2/14 (14)
	16,000	5,300	25/31 (81)	5/31 (16)
	32,000	10,600	2/2 (100)	1/2 (50)
Radon 222	4,000	2,800	4/10 (40)	1/10 (10)
	8,000	5,600	11/13 (85)	6/13 (46)
Iridium 192	18,000	5,700	3/6 (50)	2/6 (33)
	26,000	8,000	4/6 (67)	2/6 (33)

ESD = equivalent single dose.

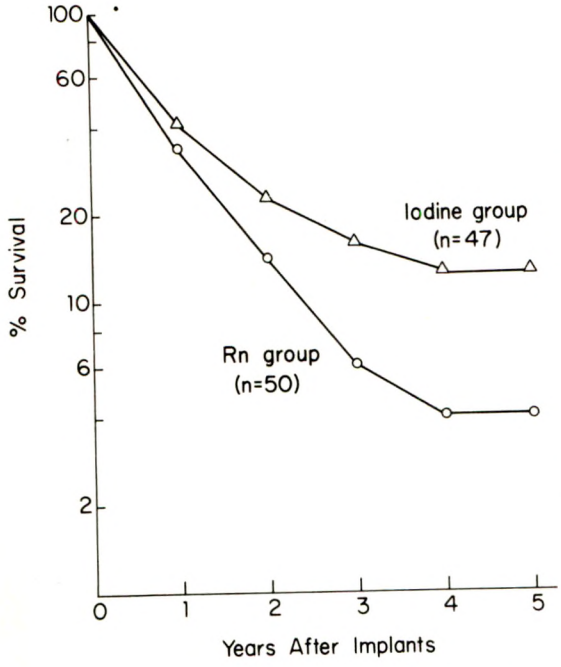

Fig. 3. The cumulative per cent survival of patients with unresectable non-apical cancer of the lung, implanted either with iodine 125 seeds or with radon 222 seeds.

better dose distribution of implanted seeds to irregularly shaped tumor volumes (Fig. 1), and a long half-life of the radionuclide (Table 1), which simplifies the problem of availability, especially on short notice.

In addition to the physical advantages, our present clinical data indicate that implants with iodine 125 have a higher therapeutic ratio than with radon or iridium. This effective local tumor control is not limited only to the malignant tumors and anatomic sites discussed in this paper. For example, the results with the iodine 125 seed implants in prostatic carcinoma and in apical carcinoma of the lung show that high local cure rates can be obtained.[6,7]

Table V

TUMOR CONTROL RATE AS A FUNCTION OF TUMOR DOSE

(Unresectable Carcinoma of the Lung)

Radioactive Seeds	Minimum Tumor Dose (rad)	Tumor Control (Per Cent)
Iodine 125	8,000 16,000	6/14 (43) 26/31 (84)
Radon 222	8,000	17/38 (45)

The optimum total minimum tumor dose with iodine seeds was found to be in the range of 16,000 rads for the average size implant; 2.5 cm. to 4 cm. average dimension (Table III). The normal tissue tolerance to this dose has been quite satisfactory, although the equivalent single dose (ESD) was estimated to be 5,300 rads. The computation of the ESD does not take into consideration time factors other than the recovery time from the sublethal radiation damage.

The apparent superior results with iodine 125 implants over other radionuclides remain to be confirmed by additional clinical work. The radiobiologic basis for such a superiority, if present, also requires study. Among many possible factors, three

Table IV

INTERSTITIAL IMPLANTS OF UNRESECTABLE CARCINOMA OF THE LUNG

	Radon 222 (1963–1968)	Iodine 125 (1968–1973)
1. Total number of implants	53	52
2. Over-all average survival in months from initial therapy*	22 (1–67)†	16 (1–63)†
3. Number of patients survived less than 4 months	15	7
4. Local tumor control rate in patients surviving 4 months or more	17/38 = 45%	30/45 = 67%
5. Complication rate	5/38 = 13%	5/45 = 11%

* Excluded the immediate postoperative death groups (3 patients in iodine and 1 in radon).
† Eight patients still alive (iodine 125); 1 patient alive (radon 222). Figures in parentheses are the ranges of the survival time.

principal explanations might be advanced to account for the effectiveness of the iodine implants. These are: (a) low dose rate; (b) a sustained continuous irradiation; and (c) a possible high RBE of low energy gamma radiation from the iodine seeds. Theoretical advantages of protracted, low-dose rate irradiation from sources having long half-lives have been postulated by Cohen.[2] He based the therapeutic advantage with permanent implants having long half-lives primarily on the differential recovery rates between tumor and normal tissues, derived from the isoeffect data on the skin tolerance dose and the tumor lethal dose of skin cancers. An additional advantage of low dose rate irradiation might stem from a lower oxygen dependency. Several cell culture studies have shown that the low dose rate irradiation (30–60 rads/hour) significantly reduces the oxygen enhancement ratio (OER).[4,8] The reasons for this are not known at the present time. Indeed, the magnitude of the OER reduction appears to be comparable with that obtained with neutron sources.[3,8] A reduction in the OER is considered to be therapeutically advantageous, because the hypoxic cells in tumors are thought to be responsible for local failure due to their high radioresistance. Secondly, continuous irradiation may be an important radiobiologic variable. The recent clinical experience of Pierquin[9] with low dose rate teletherapy suggests that continuous, low dose rate irradiation to a relatively large volume has led to a dramatic reduction in tumor size. Whether this apparent high therapeutic effect is due to continuous irradiation, to a low dose rate effect, or both, remains to be solved. The initial dose rate of iodine implants is usually maintained at least up to the first 30 days after the implant. This effect results from the fact that the implanted volume is reduced to 50 per cent in the first month (Fig. 2), and that the originally spaced sources come closer together, even though the isotope decays. Indeed, more than half of the implanted tumor is exposed to irradiation at a dose rate of about 20 per cent higher than the initial rate. The initial dose rate varies in the range of a minimum of 7 rads/hour (the total dose of 16,000 rads) up to an infinitely higher dose rate (*i.e.*, the dose in the core of the implanted tumor). Continuous irradiation apparently has some theoretic advantage over the acute fractionated therapy in a situation where the cellular proliferative activity widely varies. The work by Brown *et al.*[1] indicates that the efficacy of treatment by continuous irradiation is little altered by a drastic change in the proliferation of cells, while acute, fractionated therapy strongly depends on the cellular proliferative rate.[1]

The RBE of the iodine 125 seeds is at present undetermined. Judging from the LET spectrum of the gamma rays of iodine 125, it might be assumed that the RBE of the seeds would be slightly higher than 1 and less than 1.5. Obviously, more cellular radiobiologic studies are needed to answer this question.

CONCLUSION AND SUMMARY

Our clinical experience with interstitial tumor therapy is presented in 2 groups of patients: 98 patients with metastatic carcinoma in neck lymph nodes implanted with iodine 125, iridium 192 or radon 222 encapsulated sources, and 105 patients with primary unresectable lung tumors, which were implanted either with radon 222 or iodine 125 seeds.

The local tumor control rates with iodine 125, radon 222 and iridium 192 were 78 per cent (38/49), 65 per cent (15/23) and 58 per cent (7/12), while the local complication rates were 17 per cent, 35 per cent and 43 per cent, respectively. An analysis of the tumor control rate as a function of the implanted tumor dose shows that the iodine 125 implants with a delivery of the minimal effective tumor dose of 16,000 rads have a higher therapeutic effect than either radon 222 or iridium 192. The results of the patients with unresectable lung tumors similarly show that the implants with

iodine 125 sources are superior to those with radon 222.

The advantages could stem from the better spatial dose distribution, and from radiobiologic considerations associated with low dose rates, continuous irradiation, and possibly gains in RBE.

The present clinical data clearly demonstrate that iodine 125 seeds have a higher therapeutic ratio than radon 222 seeds. There are, in addition, distinct physical advantages making iodine 125 an attractive substitute for radon 222 for the interstitial implantation of malignant tumors.

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THE THERAPEUTIC USE OF FRACTIONATED SUBTOTAL BODY IRRADIATION*

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THE use of total body irradiation was suggested by Dessauer in 1907,[6] but the first therapeutic results were not reported until 1923.[3] In 1942 Medinger and Craver[17] published a comprehensive review of the previous reports on total body irradiation, along with an analysis of 270 cases treated by continuous irradiation of the entire body to total exposures of 50 to 300 r of 185 kV x radiation at low exposure rate (0.86 r per hour for 3 to 18 days). Despite the favorable results which were presented, and the conclusion that "total body irradiation is a useful adjunct to local roentgen therapy in the treatment of the lymphomatoid diseases," it was generally assumed that tolerable doses of radiation to the whole body would be too small to have any appreciable effect upon malignant tissues. After 1948, chemotherapy became the accepted modality for the palliative treatment of generalized malignancies. In 1953, Loeffler *et al.*[14] demonstrated that single, short exposures to 2 MV x radiation of up to 200 r in air to one side of the body caused less systemic reaction and hematopoietic depression than might have been anticipated. Because of this experience with palliation, in 1960 Robbins and Loeffler[19] treated a 19 year old male with an extensive Wilms' tumor using fractionated subtotal body irradiation with *curative* intent. The patient remained asymptomatic and free of clinical malignancy for over 4 years. The post-treatment history of this patient led the authors to treat 41 patients for cure with subtotal body irradiation (STBI), and this communication summarizes their experience.

These 41 patients have been treated since November 1, 1961 with a gradual change in fractionation schedules and modifications toward more individualized treatment. Initially, treatment was administered at 50 r midplane tumor dose per day to one field in a single series. The most recent patients have been treated at 10 to 15 r per day, depending on age, general health, and disease status, with repeated series of treatments, and with supplementary irradiation to bulky or residual localized tumor.

During this time, del Regato,[5] Saenger *et al.*,[20,21] Andrews *et al.*,[1,2] Jacobs and Marasso,[8] and Johnson[10,11] have been using other schedules and techniques for the treatment of malignant disease by total body irradiation.

This report is submitted at this time to permit a comparison of these various approaches, and perhaps to stimulate other modifications and uses.

TECHNIQUE

Forty of 41 patients were treated using 25 MeV x radiation from an Allis-Chalmers Betatron. The other patient was treated with cobalt 60. The treatments were given 5 days per week with the patient reclining on a stretcher, which permitted the arms, legs, and skull to be excluded from the rectangular field. In order to improve the uniformity of dose distribution over the large body volume, the patient was placed in 4 positions successively. They were: left side anterior; left side posterior; right side anterior; and right side posterior. An additional lead shield was placed close to the patient in order to protect the eyes (Fig. 1). The TSD varied from about 300 to about 400 cm., depending on body length. The object was to place the patient as close to the Betatron as possible to im-

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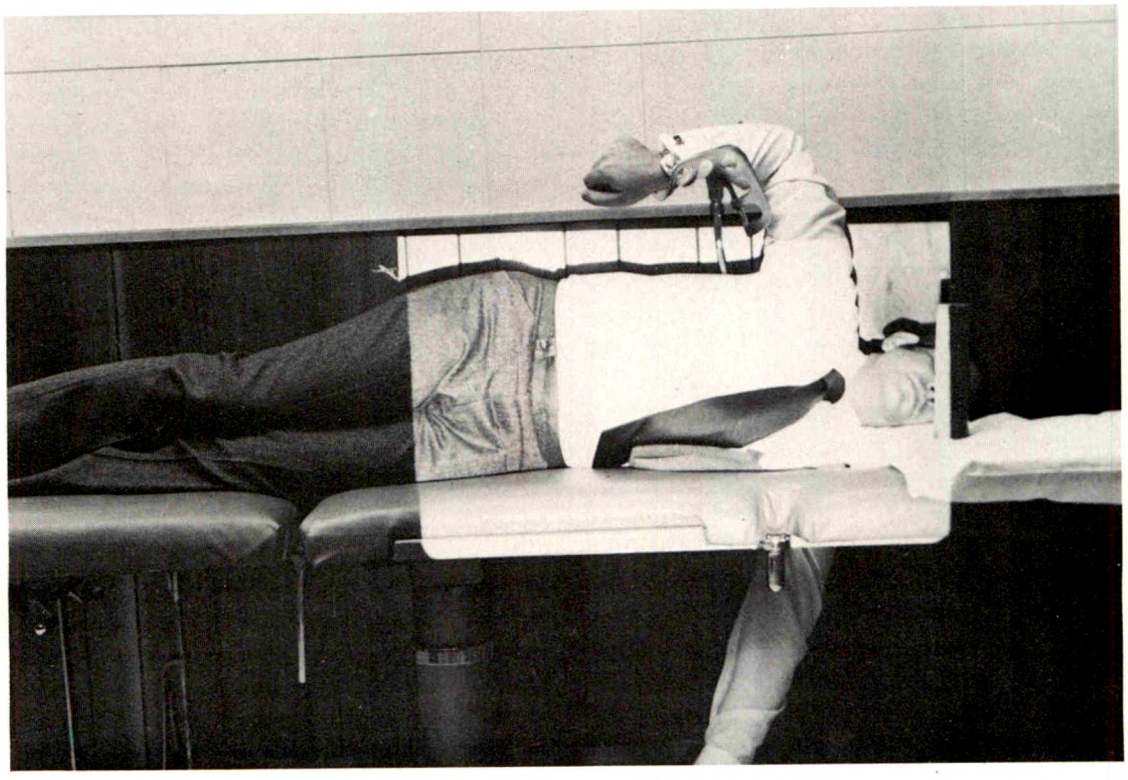

Fig. 1. Arrangement for subtotal body treatment.

prove dose rate. The exposure rate varied from 3 to 19 r per minute at the patient. The maximum thickness of the patient was used to calculate the mid-plane dose at the axis, which is given as the "tumor dose." The calculations were checked by entrance and exit measurements with selected patients, and by measurements in a water phantom, with good agreement. This arrangement could not be utilized with the patient treated on the Theratron 80 cobalt 60 unit because of the room size. Therefore, the subtotal body volume was treated in 2 fields daily, rotating the head of the Theratron 80 to simulate a single field, with constantly varying junction lines.[22] On June 1, 1971 dose recording was changed from "r" to rad.

CLINICAL MATERIAL

Thirty-nine patients with generalized (Stage III and IV) malignant lymphomas, and 2 patients with disseminated seminoma, have been treated with STBI. The current standard lymphoma staging procedure has been utilized routinely since 1970. The staging of the earlier cases was based primarily on clinical findings after biopsy in addition to routine roentgenograms, radioisotopic scans, bone marrow aspiration, liver biopsy, and cytologic examination of malignant effusions. Bipedal lymphangiography has been done regularly since 1969. All patients presented with multiple areas of lymphadenopathy representing uncontrolled disease with approximately 22 per cent (9 of 41) having received prior chemotherapy, local and regional irradiation, or a combination. No staging laparotomies were performed on any of the patients reported here. Therefore, it is possible that some patients were understaged. All tissue sections were reviewed for this presentation by one pathologist, for consistency of interpretation, and to conform to the classification of Rappaport *et al.*[18] of lymphomas and the Rye modification of the Lukes-Butler

classification of Hodgkin's disease.

Ten cases were classified as Hodgkin's disease and 29 cases as non-Hodgkin's lymphoma. Twenty-five patients were generalized Stage III and 14 were Stage IV.

Because of the heterogeneity of the disease entities, previous therapy, and STBI therapy, individual summaries are presented chronologically in Figure 2. Survival data as of September 1, 1972 are presented schematically in Figure 3. The survival data are summarized by disease entity in Table 1. The abbreviations used in this Table are:

NM—Nodular mixed histiocytic-lymphocytic
NLPD—Nodular lymphocytic poorly differentiated
NLWD—Nodular lymphocytic well differentiated
DH—Diffuse histiocytic
DM—Diffuse mixed histiocytic-lymphocytic
DLPD—Diffuse lymphocytic poorly differentiated
DLWD—Diffuse lymphocytic well differentiated
HDMC—Hodgkin's disease, mixed cell

RESULTS

The total dose ranged from 300 rads in 20 treatments to 3,000 rads in 200 treatments.

Nine patients of the initial series were treated at the rate of about 50 r daily, until the first indication of a decrease in the peripheral blood cell counts, anticipating a further decrease before recovery. However, in several patients the depression was more severe and prolonged than anticipated, probably contributing to the death of 1 patient (C.P.) from infection (72 year old male with DH with bone marrow involvement). The depression tended to be more severe and more prolonged in older patients, presumably because of decreased hematopoietic reserve despite initially normal peripheral blood cell counts. One patient with HDMC treated for systemic recurrence following localized therapy died of fungal pneumonia 28 months after STBI, with no evidence of Hodgkin's disease at autopsy. Another with HDMC treated after failure to respond to a third course of nitrogen mustard, is currently NED (no evidence of disease) and working in a factory, almost 9 years after STBI. A patient with NM presenting with general nodal involvement and a pleural effusion is living NED 92 months after treatment. The other 5 in this group died of disease from 3 to 15 months after STBI.

Nine of the next series of patients received 25 to 35 r daily in a single series. Two patients are living NED at 100 and 57 months, respectively, after STBI and a third is living NED at 82 months having had a local axillary recurrence treated at 3 years after STBI. One patient (L.H.), a 59 year old female with DLWD, refused whole blood or platelet transfusions for religious reasons, and died from bleeding 4 weeks after STBI was discontinued. The other 5 patients died with disease from 2 weeks to 29 months after STBI, 2 of these having been *in extremis* at the beginning of treatment and having failed to respond.

Since September, 1968, treatment has been administered at the rate of 28 r per day or less, and at 10 to 15 r daily since June, 1970. Patients over age 70 received the lesser daily exposure. Along with the reduction in daily exposure, the total management was modified. In the earlier groups, a single series only was administered, and the patients were then observed without further therapy. Patients demonstrating recurrence were referred for chemotherapy. Patients treated more recently have received a succession of series, each series being started when the peripheral blood cell counts have returned to normal. No further STBI therapy is given when recovery is prolonged, indicating that recovery may not follow an additional series. In addition, many of these patients have received localized supplemental irradiation to those volumes which had contained the most bulky tumor on initial examination. The total therapy has thus become more individualized. A major intent has been that the therapy will not prevent patients from continuing near-normal activities. With the lower daily exposures there are rarely any adverse reactions except for a feeling of tiredness toward the end of each series when the blood cell counts drop.

	PT	DIAGNOSIS	STAGE	EXTRA-NODAL	PREVIOUS THERAPY	DAILY TUMOR DOSE	#RX's	TOTAL TUMOR DOSE	ADDITIONAL AREAS
1.	FW	HDMC	III			50 R	34	1700 R	
2.	JW	HDMC	III		Mantle	45 R	53	2385 R	
3.	JC	HDMC	III			62 R	18	1116 R	
4.	CP	DH	IV B	Bone Marrow		50 R	19	950 R	
5.	AL	DH	IV	Pleura	HN_2	50 R	32	1600 R	
6.	EG	HDMC	III		HN_2	50 R	12	600 R	
7.	VH	HDMC	III		Mantle, HN_2	50 R	28	1400 R	
8.	CH	DLWD	III		Abdomen	50 R	20	1000 R	
9.	NB	NM	IV	Liver, Pleural Effusion	HN_2	25 R	66	1650 R	
10.	JB	HDMC	IV	Liver	HN_2	25 R	55	1375 R	
11.	LH	DLWD	III			35 R	47	1645 R	
12.	RC	NM	IV	Pleural Effusion		50 R	16	800 R	
13.	CD	HDMC	III			35 R	16	560 R	
14.	JW	HDMC	III		Mantle, HN_2	25 R	20	500 R	
15.	JS	NLWD	IV	Liver		35 R	21	735 R	Epitrochlear, Popliteal
16.	BS	NM	III			35 R	23	805 R	
17.	JL	HDMC	IV	Lung		35 R	76	2660 R	
18.	EA	NLWD	IV	Bone Marrow		25 R	20	500 R	Mediastinum, Epigastrium
19.	WZ	DM	III B			25 R	37	925 R	
20.	BD	Seminoma	IV	Lung		25-15 R	130	2810 R	
21.	AH	NLPD	III			25 R	60	1250 R	Epitrochlear
22.	VF	NLWD	III			25 R	88	1950 R	
23.	WS	NM	III			20 R	80	600 R	
24.	JM	DLWD	IV	Vertebrae		28 R	84	952 R	
25.	GS	DLPD	III			20 R	97	1940 R	
26.	TM	NLWD	III			25 R	84	850 R	Mantle, Abdomen
27.	WC	NLWD	IV	Liver		30-20-10 R	66	1240 R	
28.	WU	DM	IV	Vertebrae		10 R	102	1020 R	Lumbar Spine
29.	MR	DLWD	III			15 R	75	1125 R	
30.	DL	DLWD	III			15 R	39	585 R	Epitrochlear, Mantle
31.	RL	DLPD	III			15 R	11	165 R	
32.	EK	DLWD	III			10 R	37	370 R	
33.	AE	DH	III			15 R	107	1605 R	Mantle, Lumbar Spine
34.	WZ	HDMC	III B			15 rad	45	675 rad	Mantle
35.	HE	NLWD	IV	Bone Marrow		15 rad	90	1350 rad	
36.	BA	NLWD	IV	Spinal Canal		15 rad	90	1350 rad	Lumbo-Dorsal Spine
37.	BB	NM	III			15 rad	200	3000 rad	
38.	AI	NM	III			15 rad	20	300 rad	
39.	MB	DLWD	III			15 rad	45	675 rad	Cerebro-Spinal Axis
40.	LG	NLPD	IV	Liver, Bone Marrow	Local Fields Chemotherapy	15 rad	24	360 rad	

Fig. 2. Individual patient data.

Most of the successfully treated patients have worked during the entire course of therapy with little or no lost time. One patient (75 year old male, Stage IV, DM, NED at 28 months) is the Chairman of the Board of Directors of a large industry, and directed a major reorganization of the company during this time.

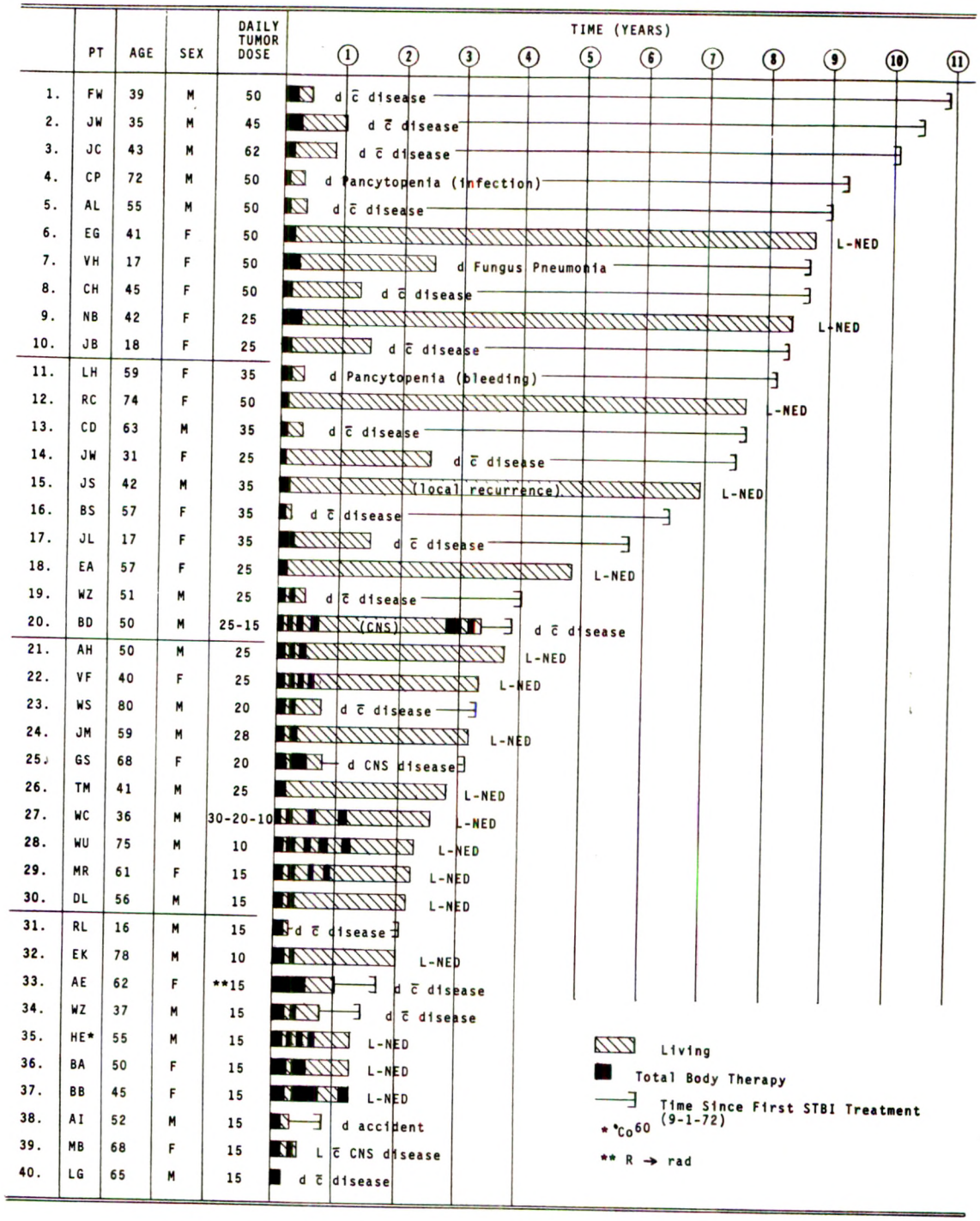

FIG. 3. Chronology since first subtotal body treatment.

Twelve of this group of 22 patients treated since September, 1968 are living NED from 4 to 43 months since the start of STBI. Two patients died within 6 weeks with no response of disease to therapy. Four had remissions, but died of recurrent disease which failed to respond to additional irradiation or to chemotherapy,

TABLE I

RESULTS OF TREATMENT BY DISEASE ENTITY

Disease (See Text)	Status—Time in Months	Living/Total
NLWD NLPD	Living NED—@ 82, 57, 45, 40, 34, 30, 15, 15 Died, disease—@ 2	8/9
DLWD DLPD	Living, NED—@ 38, 27, 26, 25 Living, disease—@ 4 Died, disease—@ 16, 8, 2 Died, complications—@ 4	5/9
NM	Living NED—@ 100, 92, 14 Died, disease—@ 8, 1½ Died, accident—@ 3	3/6
DM	Living NED—@ 27 Died, disease—@ 5	1/2
DH	Died, disease—@ 11, 4 Died, complications—@ 3	0/3
HDMC	Living NED—@ 105 Died, disease—@ 29, 18, 17, 12, 10, 5, 5, 4 Died, pneumonia—@ 28	1/10
Seminoma	Living NED—@ 104 Died, disease—@ 40	1/2
	Total:	19/41

NED = no evidence of disease.

within 1 year. One died of brain metastases without other evidence of malignancy at 8 months; and another is currently receiving treatment to the cerebrospinal axis for disease which became manifest 4 months after the beginning of STBI, presumably because of the shielding of the skull. One patient died of an accident, just prior to starting his second series with blood cell counts which had returned to normal.

Of the 2 patients with disseminated seminoma, 1 is living NED 9 years after the beginning of therapy. The other was clinically free of disease for 34 months after STBI, then demonstrated brain and lung metastases. Treatment to the brain and trunk was administered with another symptom-free period of 5 months, followed by generalized recurrence and death 40 months after the beginning of total body irradiation.

Tabulating the survivors by disease (Table 1) is suggestive. Except for 1 patient treated by STBI after other modalities had failed, all patients with NLWD and NLPD are living NED from 15 to 82 months after STBI. Conversely, only 2 of 10 patients with HDMC have had good remissions, and only 1 of these is living (and yet, at 105 months after failure of HN_2 therapy).

DISCUSSION

It is appropriate, when therapeutic results are imperfect, that both old and new methods of treatment should be constantly re-evaluated. Total body irradiation has been used intermittently for decades in the treatment of generalized radiosensitive diseases, but only recently with possible in-

tent to "cure." More commonly, generalized lymphomas have been considered to be incurable, and have been reserved for chemotherapy. Nitrogen mustard and its derivatives were used for "palliation," with limited enthusiasm. In 1953, Loeffler *et al.*[14] commented that "it is generally appreciated that higher doses are tolerated if radiation is given over a period of time. The demonstration of higher tolerance levels of total body radiation may well prove of value in the management of diseases currently being treated routinely with nitrogen mustard and its derivatives." A series of patients was then treated with specific palliative objectives,[4] and it was concluded that "no agent currently in use for the treatment of generalized cancer is offered with intent to cure . . . the principal benefit of treatment is early relief . . . of symptoms (without) severity of side effects . . . , prolongation . . . , or delayed response to treatment. In all these respects, the administration of single doses of total body irradiation has some advantage." More recently combinations of chemical agents and varied treatment schedules have been used with enthusiasm and with improved rates and durations of clinical control, occasionally with whispered talk of "cure." Whether the improved results are due to the use of combinations of agents, or to the enthusiasm with which they are being used, is being questioned, and the use of single agents with new treatment schedules is also being re-evaluated.[16,23]

As chemotherapy is becoming more effective in controlling malignant disease in the initially obvious areas, patients are surviving long enough to demonstrate new patterns of recurrence. The CNS, liver, spleen, kidneys, testes and lungs have been noted to be "sanctuary" sites in patients with acute leukemia, because of the inhomogeneous and uncontrollable distribution of chemotherapeutic agents within the body.[13] Necrotic centers of large tumors are also practically impervious to circulating chemicals. These necrotic centers also tend to be relatively radioresistant, but additional localized radiation is frequently effective in overcoming this resistance. Two of the patients reported here have demonstrated CNS disease after general remission. If the incidence of recurrence in this site becomes higher in the future, initial treatment to the brain will be considered.

The recent re-evaluation of total body radiation therapy is especially *à propos* with megavoltage radiation, with improved penetrability and decreased differential absorption, permitting dose distribution to be more uniform and more determinable than with orthovoltage radiation. Subtotal body irradiation can be considered as one portion of a spectrum of dose distribution from local field, extended field, total nodal, to true *total* body which may be chosen to encompass the known or likely extent of the malignancy. In 1960, Robbins and Loeffler[19] used fractionated subtotal body irradiation (STBI) with the anticipation of achieving a higher total dose with an improved therapeutic ratio. The head and extremities were shielded to improve hematopoietic tolerance,[9,12] assuming that these regions may be free of microscopic metastases and may be capable of hematopoietic activity. It might be anticipated that the more volume that is shielded, the higher the dose that could be delivered to the treated volume, and the greater the likelihood of control of malignancy within this volume.

The application of stress stimuli to evaluate hematopoietic reserve was suggested[15] to permit the administration of repeated therapeutic doses of total body irradiation with less risk of irreversible severe or fatal depression. The use of anoxia as a stimulus to erythropoiesis did not seem to be practical as a clinical test, and the administration of dead bacteria to produce a leukocytosis was suggested. Endotoxin and etiocholanolone are now being investigated for this purpose.[7,24]

Long remissions have been reported by Medinger and Craver,[17] and by Johnson[11] following the administration of doses that are usually inadequate to cause even

temporary control when given to small volumes. This may imply either an additive abscopal effect of radiation, or an improvement in a host "immune" mechanism of some type.

The results reported here demonstrate that long remissions can be achieved in patients with generalized lymphomas. Because of the small number of patients with heterogeneous histories and disease entities, evaluation of subgroups can only be suggestive. Except for 1 patient who was started on STBI *in extremis* after many other treatments had failed, all patients with nodular lymphocytic lymphomas, whether well or poorly differentiated, are living NED from 15 to 82 months after therapy. Johnson[11] reports excellent results using a somewhat different technique, but defines his patients as having generalized "lymphosarcoma" with less classification, preventing direct comparison. If we assume that "lymphosarcoma" includes Rappaport *et al.*[18] NLWD, NLPD, DLWD, NM and DM entities, 17 of 26 of our equivalent patients are living NED from 14 to 100 months. The patients with Hodgkin's disease have generally done poorly, but the 2 of 10 patients who were controlled (one living NED at 105 months) were both patients who had recurrence following intensive chemotherapy.

The lower-dose, repeated series approach seems to be yielding somewhat improved early control compared to the higher-dose, single-series used initially. This may not be valid, however, since the earlier patients had a higher ratio of failures of other therapy, and included most of the Hodgkin's disease cases. Nevertheless, the lower dose technique has the major advantages of being more controllable with less likelihood of complications, of causing few symptoms, and of permitting more individualization of total dose and of supplementary localized radiation. Many of the last series have continued normal activities over the entire clinical course, taking time only to receive the daily treatment as part of the normal daily routine. This therapy technique would be less acceptable if the patients had to travel great distances or be transposed elsewhere to receive the treatments, but is no problem at the community level. Our chemotherapeutic confreres have indicated sufficient interest in the results presented here, that a combined prospective study has been started to treat Stage IV non-Hodgkin's lymphomas by this technique as the initial mode of treatment.

CONCLUSIONS

A technique is presented for the treatment of generalized radiosensitive malignancies. The results of fractionated STBI (subtotal body irradiation) in a group of 41 patients are at least as satisfactory as those achieved by any other therapeutic modality.

Eight of 9 patients with generalized Stage III and IV nodular lymphocytic lymphoma, both well and poorly differentiated, are living without evidence of disease, from 15 to 82 months since treatment.

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The authors wish to thank Dr. Frank P. Urso of the Department of Pathology, Akron City Hospital, Akron, Ohio, for collecting and reviewing the original biopsy material of these patients, and re-classifying them when necessary to conform to the Rappaport and Lukes categories.*

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* On April 24, 1974, the day this paper was presented in Hawaii, a 49 year old white male with Stage III NLWD lymphoma received the 267th treatment of 15 rads in a series which had started on April 9, 1973—for a total of 4,000 rads. This patient had presented with prominent lymphadenopathy of the pre-auricular, cervical, supraclavicular, axillary, hilar and inguinal regions, and palpable retroperitoneal masses. Laparotomy was performed, with positive retroperitoneal lymph node biopsy, splenectomy, and liver biopsy which was negative. After 4 weeks of STBI, 300 rads, all palpable disease had disappeared. He worked every day thereafter, 6 days per week, as a steel grinder, receiving his daily treatments on the way home from work. His blood cell counts never dropped below normal ranges during this time. Therapy was discontinued because the dose delivered seemed adequate, and because of uncertainty over late effects. He was asymptomatic, NED, on November 7, 1974.

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THE RADIUS-DOSE RELATIONSHIP IN LINEAR SOURCE THERAPY*

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THE cylindrical applicator containing a central linear source has been used successfully in the past to treat superficial disease in the vagina, as well as other body cavities. Experience has shown that high surface doses are tolerated when small vaginal cylinders, colpostats, or ovoids are used, whereas the surface dose must be reduced when large applicators are employed.[2,4]

The purpose of this communication is to present a theoretical relationship between the tolerance dose on the surface of a cylindrical applicator containing a central linear source and the applicator radius.

TECHNIQUE

In 1947 Jolles and Mitchell[3] proposed that the skin tolerance dose for an x-ray field varies inversely with the cube root of the ratio of the area of skin irradiated to the length of its bounding perimeter. Later Cohen[1] expanded the concept and stated that for irradiation of a portion of an organ, the tissue tolerance dose varies inversely with the cube root of the ratio of the volume of tissue irradiated to the area of its bounding surface, or, symbolically

$$D = K(V/A)^{-0.33}, \qquad (1)$$

where D is the tissue tolerance dose, V is the volume of tissue irradiated, A is the area of bounding surface, and K is the constant of proportionality. For an open-ended, hollow cylinder of tissue (Fig. 1), Equation 1 may be expressed in terms of radii as follows:

$$D = K\left(\frac{R_d^2 - R_s^2}{2R_d}\right)^{-0.33}, \qquad (2)$$

where R_s is the radius of a cylindrical applicator containing a central linear source, and R_d is the radius to the depth of the percentage depth dose criterion. If we let C equal the ratio R_d/R_s, Equation 2 may be written in terms of R_s,

$$D = K\left[R_s\left(\frac{C^2 - 1}{2C}\right)\right]^{-0.33} = K'R_s^{-0.33}. \qquad (3)$$

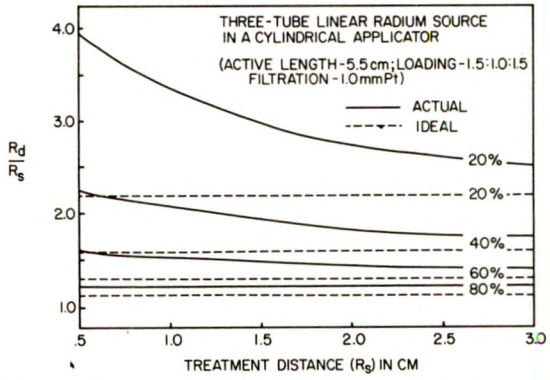

FIG. 1. Cross section of an open-ended, hollow cylinder of irradiated tissue. R_s is the radius to the surface of a cylindrical applicator from the central linear source, and R_d is the radius to the limit of the irradiated tissue at the percentage depth dose criterion.

The validity of Equation 3, the radius-dose relationship, depends on the constancy of the ratio R_d/R_s for every value of R_s, the treatment distance, at each percentage depth dose criterion. In Figures 2 and 3; and Tables I and II the constancy of the ratio R_d/R_s is examined for 2 linear sources having active lengths of 1.5 cm. and 5.5 cm. All doses were calculated opposite the center of the linear source. The broken horizontal lines show the relationship for an "ideal" situation in which dose varies inversely with the square of the distance from the source. It can be seen in Figure 2 and Table I that the value of the ratio R_d/R_s is remarkably constant for the

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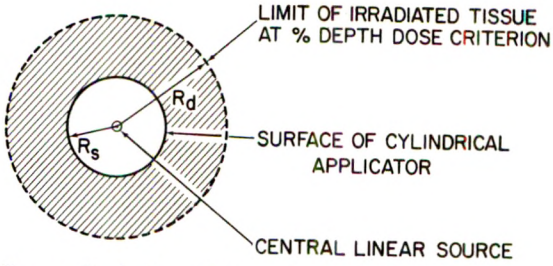

FIG. 2. Variation of the ratio R_d/R_s with treatment distance, R_s, for a single-tube central linear radium source in a cylindrical applicator. The percentage depth dose criterion used for each curve is indicated.

1.5 cm. linear source for treatment distances greater than 1.0 cm. Although the relationship is not as "ideal" for the 5.5 cm. source, the R_d/R_s values are still reasonably constant for treatment distances over the clinical range of 1.5–2.5 cm., particularly for the higher percentage depth dose criteria (Fig. 3; and Table II).

In Table III the relative tolerance dose for cylindrical applicators of various diameters has been calculated using the radius-dose relationship (Equation 3). It is pertinent to note that, although depth dose is decreased with short treatment distances, the tolerance dose is increased.

SUMMARY

The rationale and physical data are presented which support the hypothesis that

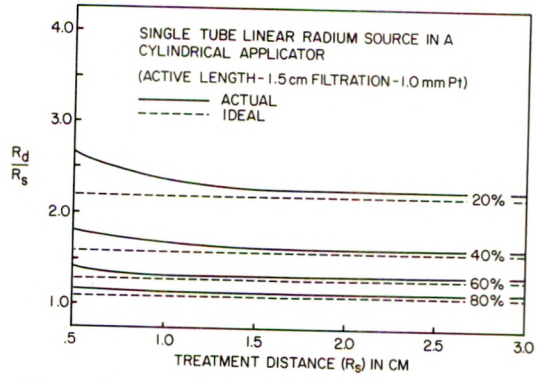

FIG. 3. Variation of the ratio R_d/R_s with treatment distance, R_s, for a three-tube central linear radium source in a cylindrical applicator. The percentage depth dose criterion used for each curve is indicated.

TABLE I

R_d/R_s RATIOS FOR A SINGLE-TUBE, LINEAR, RADIUM SOURCE IN A CYLINDRICAL APPLICATOR

(active length—1.5 cm.; filtration—1.0 mm. Pt)

Treatment Distance R_s (cm.)	Percentage Depth Dose Criterion			
	20	40	60	80
0.5	2.66	1.80	1.40	1.16
1.0	2.39	1.66	1.33	1.14
1.5	2.31	1.63	1.31	1.13
2.0	2.28	1.61	1.30	1.13
2.5	2.26	1.60	1.30	1.12
3.0	2.25	1.59	1.30	1.12

TABLE II

R_d/R_s RATIOS FOR A THREE-TUBE, LINEAR, RADIUM SOURCE IN A CYLINDRICAL APPLICATOR

(active length—5.5 cm.; loading—1.5:1.0:1.5; filtration—1.0 mm. Pt)

Treatment Distance R_s (cm.)	Percentage Depth Dose Criterion			
	20	40	60	80
0.5	3.96	2.26	1.58	1.22
1.0	3.37	2.11	1.56	1.21
1.5	2.99	1.95	1.48	1.19
2.0	2.75	1.85	1.43	1.18
2.5	2.61	1.77	1.39	1.16
3.0	2.51	1.73	1.37	1.15

TABLE III

RELATIVE TOLERANCE DOSE ON THE SURFACE OF A CYLINDRICAL APPLICATOR CONTAINING A CENTRAL LINEAR SOURCE

Applicator Diameter (cm.)	Relative Tolerance Dose
3.0	1.100
3.5	1.045
4.0*	1.000
4.5	0.966
5.0	0.929

* The standard applicator diameter is 4 cm.

the tolerance dose on the surface of a cylindrical applicator containing a central linear source is inversely proportional to the cube root of its radius.

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X-RAY DEPTH DOSES FROM LINEAR ACCELERATORS IN THE ENERGY RANGE FROM 10 TO 32 MeV*

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IN the last 20 years there has been a continual trend towards the use of higher energy x-ray machines in the 20–30 MeV range for radiotherapy. There is some evidence by Allt[1] that the higher depth dose of such machines can improve the cure rate in the treatment of certain tumors. The major advantage of linacs over betatrons is their high dose rate (1,000 *versus* 100 rads/min. at 1 meter). Since the price of linacs increases with their maximum electron beam energy, it is important to optimize the design of components to produce the highest effective x-ray energy at a given electron beam energy and thus minimize the cost. The target and flattening filter are 2 components, whose optimization has been neglected by manufacturers of modern linear accelerators used in radiotherapy.

In a recent paper, Rawlinson and Johns[12] showed that a 25 MeV linac (Varian Clinac-35) produced an inferior beam of photons to a 25 MeV betatron (Allis Chalmers). In fact, from a depth dose point of view, the linac's beam was equivalent to the beam produced by the betatron when it was operated at 16 MeV. The reasons for this were attributed to differences in the design of the target and the flattening filter in the 2 machines. The betatron employs a thin tungsten target and an aluminum flattening filter, while the linac uses a thick tungsten target and a tungsten flattening filter.

The results of a further investigation of this problem showed[11] that a 25 MeV linac employing an aluminum thick target and an aluminum flattening filter produces a photon beam, whose depth dose distribution is similar to that produced by a 25 MeV betatron. We concluded that targets and flattening filters for high energy linacs should be made of *low* rather than high atomic number materials. This conclusion, however, was based on experiments done with 25 MeV electrons and does not necessarily apply when lower energy electrons are used to produce the x rays.

In this paper we investigate the properties of x-ray beams produced by electrons from 10 to 32 MeV using various combinations of targets and flattening filters. We find that at energies above 15 MeV the most penetrating beam is produced by a *low* atomic number target and a *low* atomic number flattening filter combination in accordance with previous results,[11] but that at energies below 15 MeV one should use a *high* atomic number target and *low* atomic number filter.

Another problem which has not received sufficient attention is the optimum target thickness. The x-ray yield in the forward direction and the penetration of the x-ray beam both depend on the target thickness in such a way that an improvement in one by a change in target thickness worsens the other. We have found that the optimum target thickness is approximately equal to the mean electron range in the target material. The targets then yield x-ray beams that have near optimum depth dose characteristics in addition to a good x-ray yield.

Finally, we compared high energy x-ray beams to lower energy ones, from a treatment point of view, by studying the effects of beam energy on physical parameters such as average dose and integral dose. We conclude that for the treatment of tumors near the center of the patient, beams produced at ~25 MeV are better than those in the 5–10 MeV range.

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EXPERIMENTAL

Our Varian Clinac 35 accelerator was the source of high energy electrons for this investigation using the apparatus described earlier.[11] Depth dose measurements were made using electron energies of 10.1, 15.1, 20.2, 25 and 32 MeV, with targets of lead and aluminum of the thicknesses shown in Figure 1. These thicknesses are 110 per cent of the mean electron ranges tabulated by Berger and Seltzer.[2,3]

The flattening filters were conically shaped with a base diameter of 12 cm and a height of 3.4 cm and 25 cm for the lead and aluminum filters, respectively. The filters were originally designed to flatten a 25 MeV x-ray beam to within ±10 per cent over a field of diameter 40 cm at a phantom depth of 10 cm and a source to chamber distance of 100 cm. At energies higher or lower than 25 MeV the same filters, of course, cannot be expected to flatten the beams to a diameter of 40 cm, but it turned out that they adequately flattened the beams to at least 10 cm diameter at all electron beam energies in the range from 10 MeV to 32 MeV. Since the collimator used in the present experiments was designed to give a 10 cm diameter field at an SSD of 100 cm we decided against designing a set of new flattening filters for each electron beam energy and thus used the same set of filters at all energies.

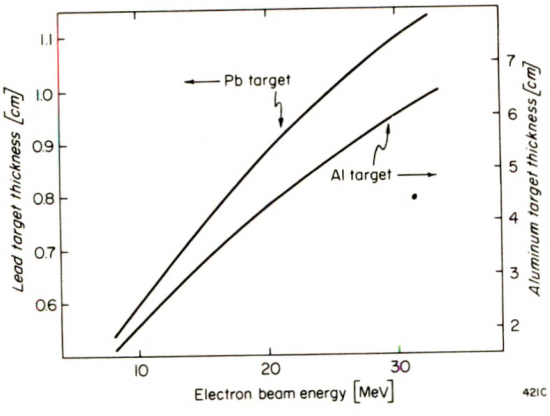

FIG. 1. The thicknesses of aluminum and lead targets used in our experiments. They correspond to 110 per cent of the mean electron range as tabulated by Berger and Seltzer.[2]

Any electron beam energy in the range from 10 to 35 MeV is obtainable from the Clinac 35 by adjustment of the current in the 57° bending magnet, provided the proper conditions are set for the RF power, the beam focussing and steering coils, and quadrupole lenses. The 57° bending magnet was calibrated using the (γ, n) energy thresholds[4,6,13] in ^{63}Cu (10.8 MeV), ^{16}O (15.6 MeV) and ^{12}C (18.7 MeV). Energies determined in this way agreed to within ±0.1 MeV with the calibration curve supplied by Varian. Hence, Varian's curve was used in the region above 20 MeV where no suitable threshold detectors are available. We estimate that the energies below 20 MeV are accurate to within ±0.1 MeV, while above 25 MeV the accuracy is about ±0.3 MeV.

RESULTS AND DISCUSSION

DEPTH DOSE MEASUREMENTS

In this section we present depth dose data for x-ray beams produced in lead (high atomic number, $Z=82$) and aluminum (low atomic number, $Z=13$) targets by electrons with energies from 10 to 32 MeV. Our results are summarized in Figure 2, where we show the percentage depth dose under a variety of conditions as a function of electron energy. The following conclusions can be made:

(i) The percentage depth dose at a given depth rises monotonically with electron energy for all target and flattening filter combinations;

(ii) At all energies above 10 MeV and probably above 6 MeV, a lead flattening filter is inferior to one made of aluminum. Thus a low atomic number flattening filter should be used in linear accelerators;

(iii) The optimum target material depends on the energy. For energies above 15 MeV a low atomic number target is preferable, while below 15 MeV targets should be made of high atomic number materials;

(iv) At energies above 25 MeV the graph for the lead target/lead flattening

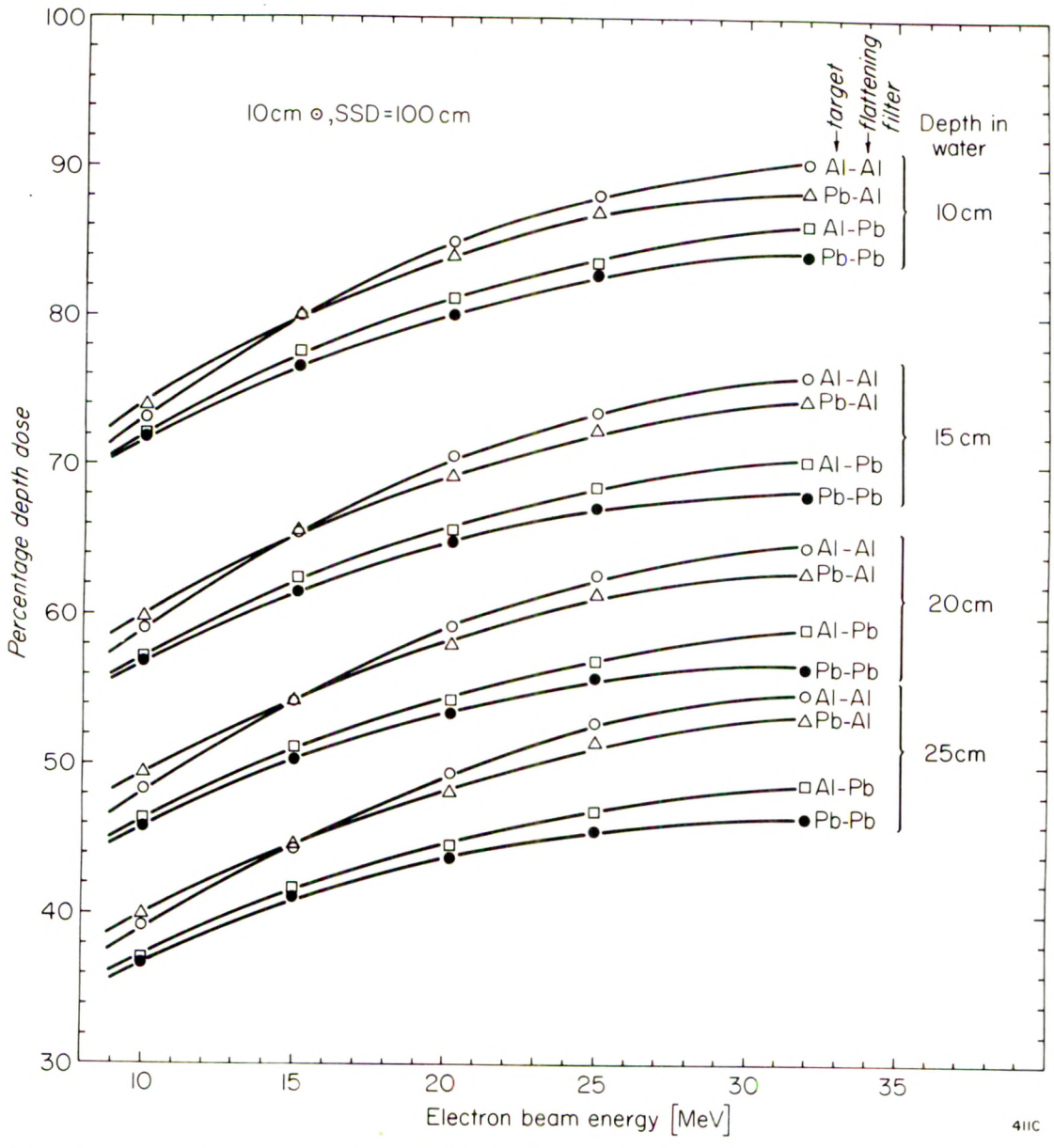

FIG. 2. Percentage depth dose at various depths in water as a function of the electron beam energy for various target and flattening filter combinations. Circular field of 10 cm diameter at an SSD of 100 cm.

filter combination is nearly horizontal, so that the percentage depth dose is almost independent of energy. Under these conditions the beam properties depend much more on the target and flattening filter material than on the electron energy. Thus for targets and flattening filters made of a high Z material, an increase in the electron energy beyond ~30 MeV has little or no effect on the x-ray depth dose distribution.

(v) The existing high energy linear accelerators manufactured by Varian and CSF could be improved considerably by replacing their high Z target and flattening filters by ones made of low Z materials.

(vi) A 25 MeV linac with target and filter of a high Z material produces the same depth dose as would an optimally de-

TABLE I

BEST AND WORST TARGET/FLATTENING FILTER COMBINATIONS AT VARIOUS ELECTRON BEAM ENERGIES

(Z is atomic number)

Electron Beam Energy, E	Target/flattening filter combinations			
	Worst		Best	
	Target	Flattening filter	Target	Flattening filter
E<15 MeV	High Z	High Z	High Z	Low Z
E≃15 MeV	High Z	High Z	High or Low Z	Low Z
E>15 MeV	High Z	High Z	Low Z	Low Z

signed linac operating at 16 MeV.

Some of the conclusions from Figure 2 are summarized in Table 1.

The percentage depth doses of various high energy x-ray beams are shown in Figure 3. The dashed curves were taken from depth dose tables,[4] and are shown for comparison, while the solid curves represent our experimental data obtained at a given energy with the best target/flattening filter combination as suggested by Table 1. It is interesting to note that curve

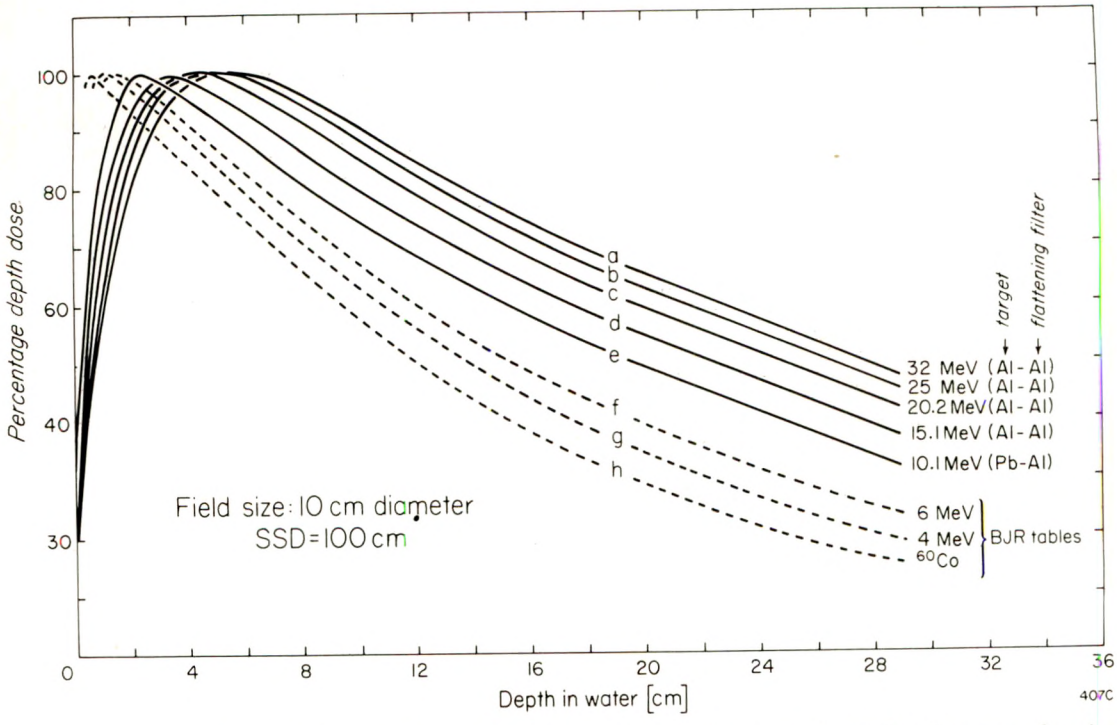

FIG. 3. Percentage depth dose curves in water of flattened x-ray beams produced by electrons of various energies. The solid curves represent our experimental data with the target and flattening filter shown in parentheses. The dashed curves are taken from tables[4] for comparison. Circular field of 10 cm diameter at an SSD of 100 cm.

(d) obtained with an aluminum target and aluminum flattening filter at 15 MeV is almost identical to the depth dose distribution of the x-ray beams produced by the commercially available 25 MeV linacs manufactured by Varian and CSF.

TARGET THICKNESS

All the depth dose data presented above were measured using thick targets; *i.e.*, targets whose thicknesses are approximately equal to R, the mean electron range in the material (Fig. 1). Under these circumstances the electron beam is completely stopped by the target and no transmitted electrons reach the flattening filter or the phantom.

We now discuss the effects of target thickness on the depth dose distributions. In Figure 4, *a* and *b*, the ion chamber current is plotted *versus* the depth in water for unflattened x-ray beams produced when 25 MeV electrons bombard targets of various thicknesses of lead and aluminum. For the thinner targets, the ion current is peaked at small depths and falls off rapidly. This peak is due to the absorption in the phantom of electrons transmitted through the target. This electron contamination is gradually removed as the target thickness

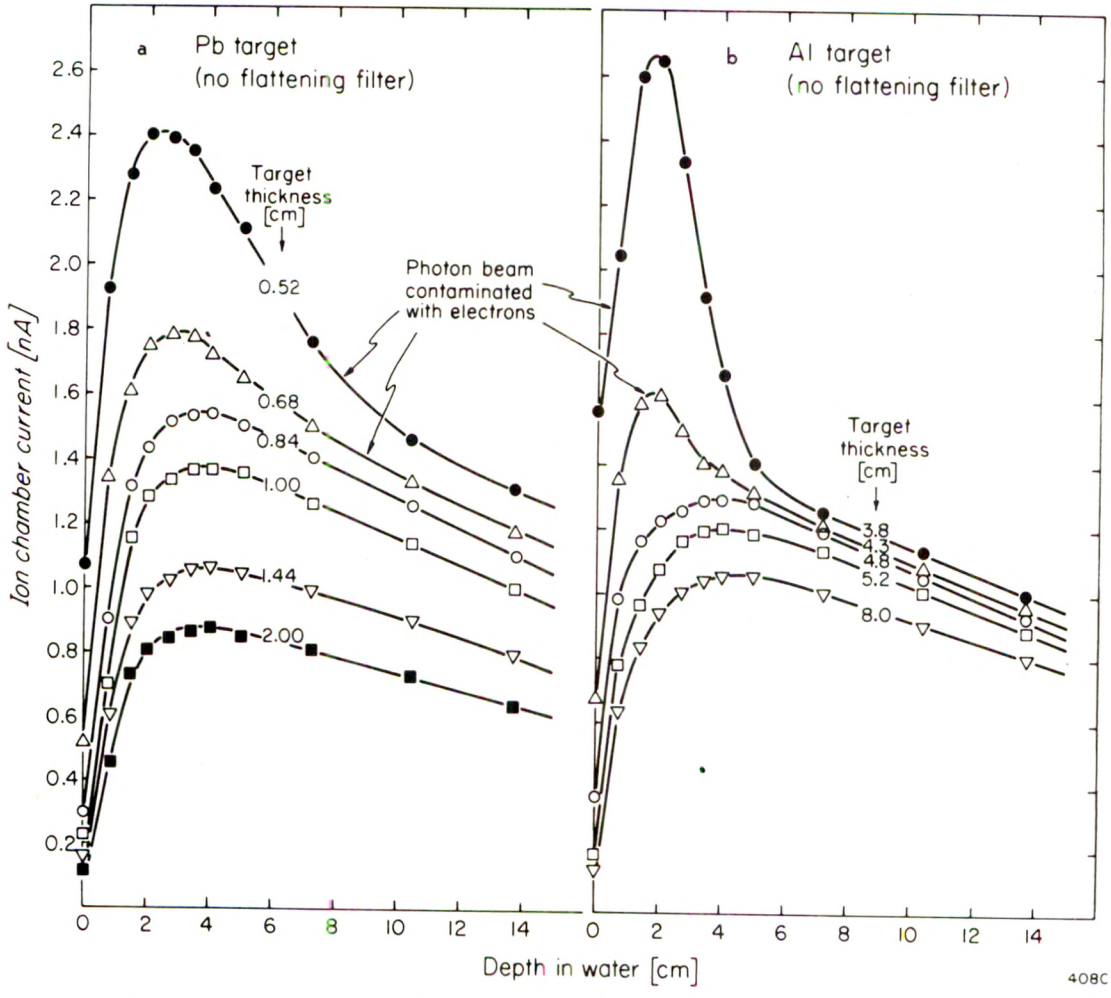

FIG. 4. Ion chamber current *versus* depth in water for unflattened x-ray beams produced in targets of various thicknesses of (*a*) lead, and (*b*) aluminum. Circular field of 10 cm diameter at an SSD of 100 cm. Electron beam energy: 25 MeV.

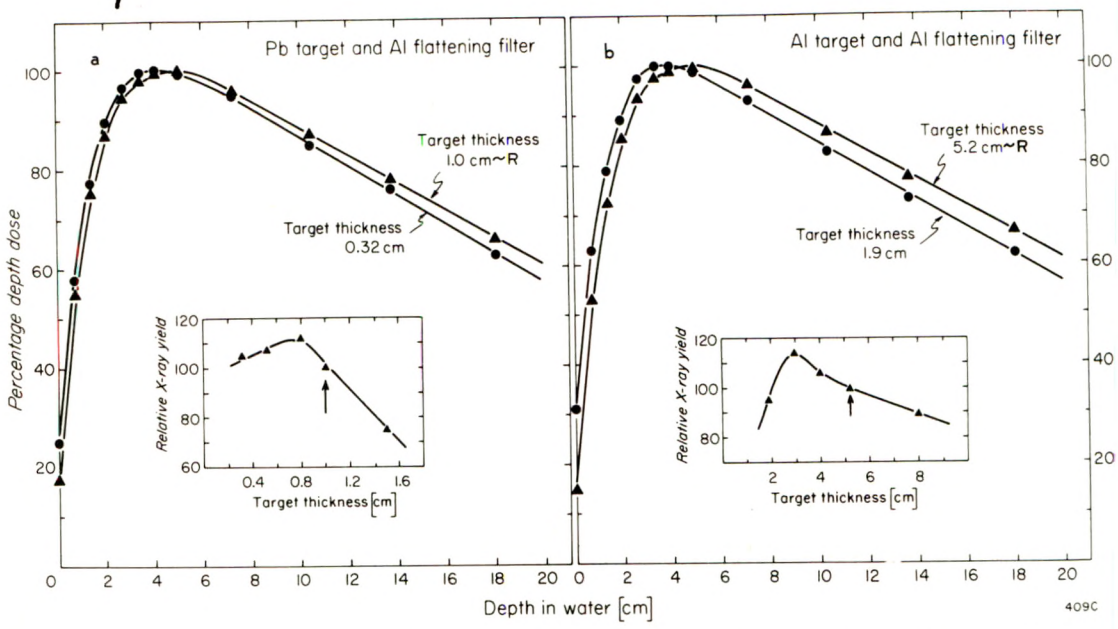

FIG. 5. Percentage depth dose curves of x-ray beams flattened with an aluminum filter for 2 target thicknesses (1/3 R and R) of (*a*) lead, and (*b*) aluminum. Circular field of 10 cm diameter at an SSD of 100 cm. Electron beam energy: 25 MeV. The inserts in the Figure show the relative x-ray yield of the target and flattening filter combinations for various target thicknesses.

is increased. When target thickness reaches the range R (about 1 cm of lead or about 5 cm of aluminum) the initial peak is completely removed showing that no electrons are transmitted through the target. These thicknesses are similar to the values shown in Figure 1. As the target thickness is increased beyond the range, the depth dose curves remain unaltered in shape but the x-ray yield decreases.

From the above considerations it is evident that electrons must be removed from the beam if a satisfactory depth dose distribution is to be achieved. It is conceivable, however, that a more penetrating photon beam would be produced if thinner targets were used, provided the electrons transmitted through the target could be removed. Indeed, there is some evidence[12,14] to show that the spectrum from very thin targets (~0.02R) is harder than that from thick targets. In addition, Lanzl and Hanson[6] and Murray[9] have shown that the x-ray yield in the forward direction is largest when targets of an intermediate thickness (~0.1R) are used. Thus it is possible that a thin target would yield a more penetrating beam and also a more intense one than a thicker one. However, the gain in intensity to be expected is not large, since Murray[9] has shown that the maximum yield which occurs at ~0.1 R is only a factor of 2 larger than the yield at either .01R or R.

In order to investigate thin targets it is necessary to solve the practical problem of removing the contaminating electrons from the beam. One possible approach is to allow the transmitted electrons to be stopped by the flattening filter. This would increase the size of the focal spot by x-ray production in the filter and thus complicate the problems of collimating the x-ray beam. We have, nevertheless, investigated the characteristics of the x-ray beams produced in this manner. Figure 5 shows measured depth dose curves and yield from targets of lead and aluminum using an aluminum filter to flatten the x-ray beam *and* to stop the electrons transmitted through the target. The depth doses obtained when the target thickness is equal

to R are compared to those given by target thicknesses of ~1/3R. Curves given by thicknesses between 1/3R and R were found to lie between the 2 extremes shown in the figure. The data show that the use of a target of thickness less than R, with the transmitted electrons stopped in the flattening filter, produces a slightly less penetrating beam than does a thick target. Furthermore, the insets of Figure 5, *a* and *b*, show that the yield can only be increased by some 15 per cent by using a target slightly thinner than R.

An alternative method of removing the electron contamination is to sweep the transmitted electrons out of the beam using a magnetic field. We therefore used a very thin (~0.01R) tungsten target and a permanent magnet (~5,200 Gauss) to sweep the electrons into a beam dump. After flattening the beam with aluminum, the depth doses were essentially no different from those obtained with a thick low Z target and low Z flattening filter and are therefore not shown.

We conclude that the advantage to be gained in using thin targets in linear accelerators over thick targets of the right material is at best small, and is outweighed by the practical difficulties involved in their use.

OPTIMUM ENERGY FOR THE TREATMENT OF DEEP SEATED TUMORS

In Figure 3 we showed the depth dose obtainable for a variety of beams produced between 4 and 32 MeV. As the energy increases the depth of the peak dose increases and so does the depth dose at points beyond this peak. The question could well be asked, whether this improvement in depth dose is worth while clinically. To answer this question, of course, requires clinical trials, and these take years. There is some evidence by Allt[1] in treating Stages IIb and III of cancer of the cervix to suggest that the betatron can give a higher cure rate than cobalt 60. Unfortunately, a number of parameters other than the radiation were altered between the 2 studies, so no really firm conclusions could be drawn. Hence, at the moment we must rely on physical arguments.

We now enquire if there are any physical parameters that can be used to select the optimum type of radiation for a given treatment. Figure 6*b* shows 4 of the depth dose curves from Figure 3 normalized to 100 per cent at a depth of 12.5 cm which is a point halfway through a patient of thickness 25 cm. From this graph it is not immediately evident which is the best radiation. The cobalt beam delivers much *more* radiation to healthy tissues in front of the tumor and much *less* radiation beyond the tumor, whereas the higher energy beams tend to produce relatively less radiation in front of the tumor and relatively more beyond it. In any case, neither beam alone would be considered a satisfactory beam to treat a deep seated tumor. The way to overcome this, of course, is to use more than one beam and the simplest arrangement is to use a parallel opposing pair. When this is done we obtain the distribution shown in Figure 6*a*. When the data are plotted in this way, it is clear that the higher the energy of the beam the less radiation is deposited in the healthy tissues outside the tumor volume.

Another parameter which could be used to assess the usefulness of a beam is the integral dose.[5,8,15] Presumably, it should be minimized for a given tumor dose. Figure 7*b* shows the integral dose as a function of the energy of the radiation, for a tumor dose of 100 rads at a depth of 12.5 cm in the patient of thickness 25 cm. This integral dose applies to either Figure 6*a* or 6*b*. From this graph it is clear that the higher the energy the lower the integral dose, in agreement with the earlier work of one of the authors.[15] However, the difference over the complete energy range from cobalt 60 to 32 MeV is not spectacular, since the integral dose decreases by only 10 per cent over this energy range.

Another parameter which could be used is the average dose along the central axis for a tumor dose of 100 rads, and this is shown in Figure 7*a*. Over the same energy

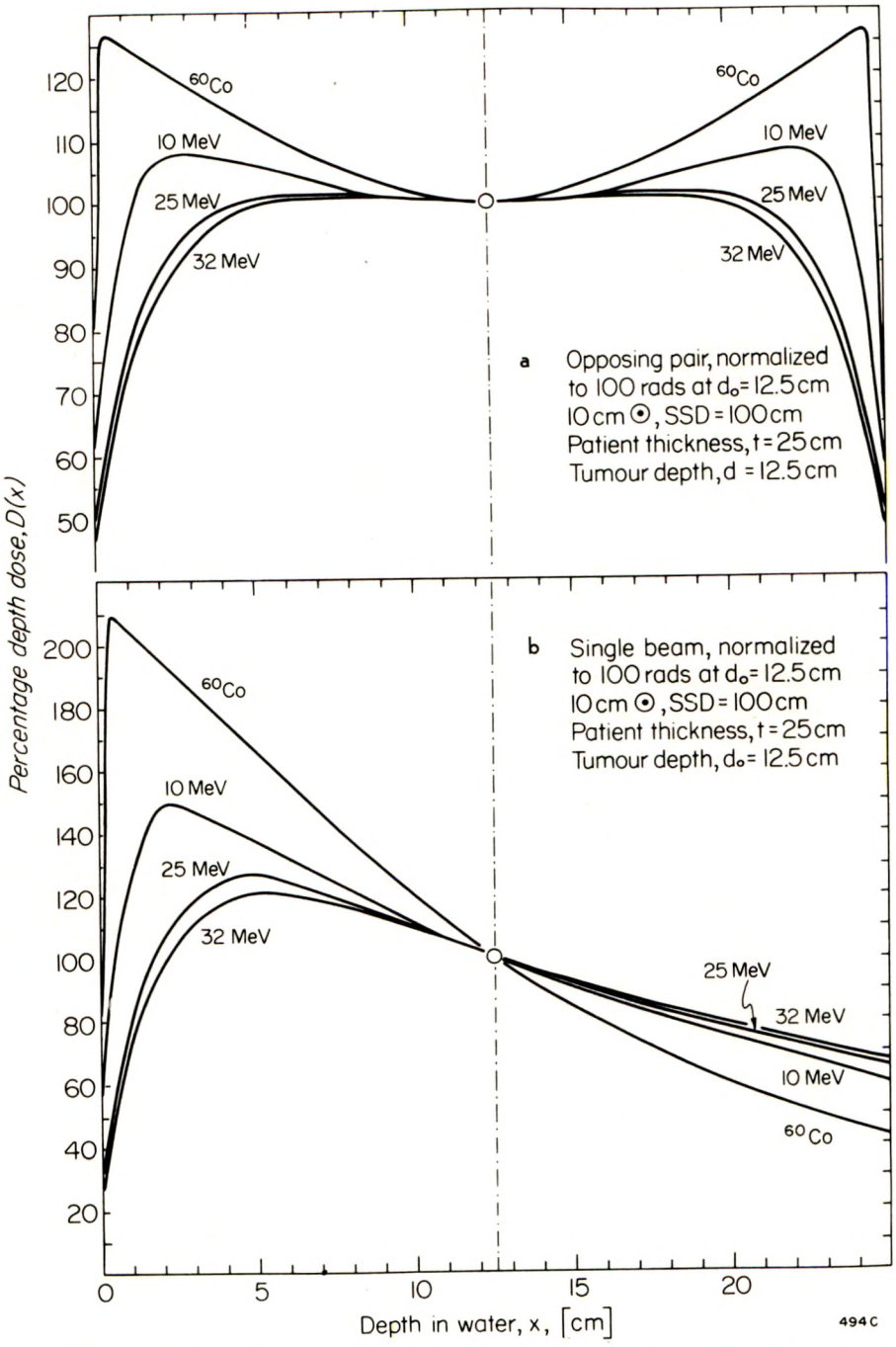

FIG. 6. Depth dose curves for ^{60}Co, 10, 25 and 32 MeV beams normalized to 100 rads at a depth of 12.5 cm. (*a*) Opposing pair, and (*b*) single beam. Field size: 10 cm diameter at an SSD of 100 cm. The data are plotted for our experimentally determined depth doses using the optimum target and flattening filter combination at a given energy.

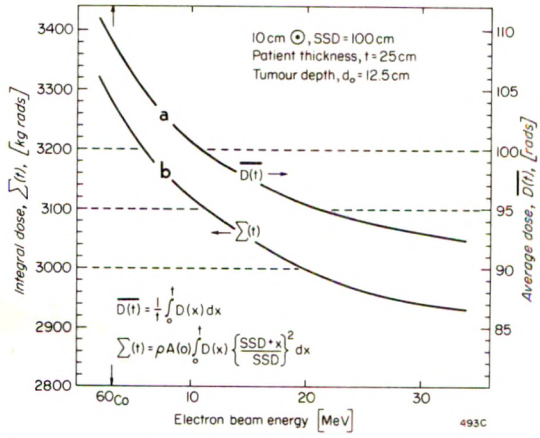

FIG. 7. Average dose along the central axis (*a*), and integral dose (*b*) as a function of the electron beam energy, when a point at the center of a 25 cm thick patient is given a dose of 100 rads. Field size: 10 cm diameter at an SSD of 100 cm.

range, it varies by about 20 per cent and decreases as the energy of the radiation increases.

These 2 parameters are mathematical ways of describing the amount of radiation received outside the tumor volume relative to the tumor volume. Calculations are shown for a point at the center of a patient, 25 cm thick. However, detailed calculations, which are not shown here, show that if a tumor is off center, or the patient is of a different thickness, the same conclusions apply. The higher the energy the more the radiation may be concentrated in the tumor volume. The improvement is a continuous one from 4 MeV up to 32 MeV: 6 MeV is better than 4, 10 better than 6, 18 better than 10, 25 better than 18, and 32 is better than 25 MeV, but the rate of improvement decreases as the energy is increased (Fig. 7, *a* and *b*).

The choice of the optimum energy is difficult. One has to balance the advantages of high energy against cost and increased complexity (such as problems with beam flatness, stability, reliability) as the energy is raised. We feel that an energy of 25 MeV is a compromise solution, taking into account these factors. Regardless of the energy, the target and filter *should* be designed to give the optimum beam.

SUMMARY

The depth dose characteristics of the x-ray beam from a linear accelerator have been studied in the electron energy range from 10 to 32 MeV for various target and flattening filter combinations.

At all energies the most penetrating x-ray beam is obtained with a low atomic number flattening filter. At energies below 15 MeV a high atomic number target should be used, while at energies above 15 MeV a low atomic number target should be employed to get the best depth dose distribution. The optimum target thickness is approximately equal to the mean range of electrons in the target material.

The study of some physical parameters such as depth dose, average dose, and integral dose, suggests that the optimum energy for linear accelerators used in the x-ray mode is about 25 MeV.

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AN "INSTANTANEOUS" DISPLAY LINEAR ACCELERATOR FIELD FLATNESS MONITOR*

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THE dosage pattern within a patient undergoing external beam x-ray therapy is usually calculated assuming uniform irradiation incident on any treatment area, and that this distribution is stable with time.

The common use of Linear Accelerators in radiotherapy, especially the "second" generation, the "bent beam" units, requires that many parameters must be adjusted and then held within narrow limits if the calculations mentioned above are to be valid.

Such parameters as microwave power and frequency, accelerating guide temperature, the electron current, steering, focusing, and bending must remain stable, otherwise large variations in the beam intensity distribution will occur.

The effect on the output of a Linac, as parameters are varied, is commonly demonstrated by traversing a single x-ray detector across various axes in a plane perpendicular to the central ray.[2] After a parameter adjustment, its effect is determined by a detector traverse. This adjust and measure sequence is tedious and time consuming. Other systems,[1] while using different techniques, still require considerable time to obtain a set of readings, and hence to adjust the beam flatness.

It was for this reason that the "instantaneous" (minimal delay) display system was developed, in which the effect of an adjustment can "immediately" be seen on a Cathode Ray Oscilloscope (CRO) screen.

It can also show any variation in beam instability against time, especially during the stabilizing period of the Linac immediately after the commencement of each exposure. This period could be a significant fraction of the patient's treatment time.

The system consists of 16 ion chambers and amplifiers, the outputs of which are sequentially sampled and displayed on a CRO. The ion chambers are spaced at 17 mm. intervals across a diameter of the field (90 cm. SSD) so that the chambers on each extremity are just in the flat portion of the beam. The ion chambers consist of used 0.22 inch cartridge cases which give a chamber of 5.3 mm. diameter by 14 mm. long. These are mounted in a block of Perspex 330 mm.×64 mm.×32 mm., the cross-section of which is shown in Figure 1. The center electrode of the ion chamber is the center conductor of 7/.029 inch insulated electrical wire, which passes down the inside of a brass tube of 0.25 inch outside diameter, and through the Perspex end cap. The other end of the brass tube passes through a pot-lock and has the amplifier chassis clamped to it. This method of construction allows the amplifier, brass tube, and ion chamber center electrode, to be removed from each ion chamber independently for servicing.

The amplifier circuit is shown in Figure 2. This consists of a dual MOSFET followed by a 741 I.C. operational amplifier, the 1 Kohm potentiometer in the feedback loop acting as a calibration (preset) gain control, and the other potentiometer as the offset control. The feedback time constant is chosen so as to remove jitter from the display, and yet be short enough to allow flatness variations to be seen with minimal delay.

The X-axis display (Fig. 3) consists of an oscillator (7400 and 7410) which drives a 4 bit binary counter (7493). The outputs of this counter then select the appropriate

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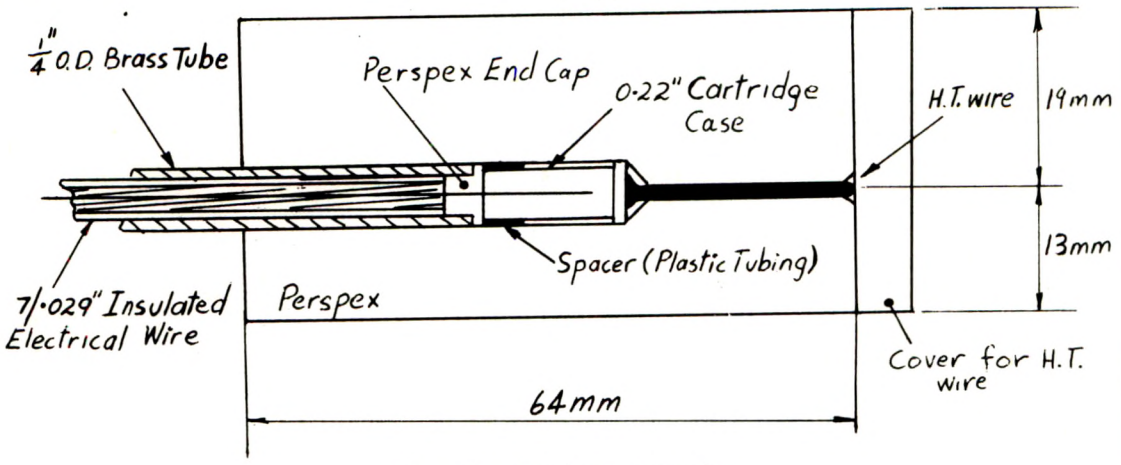


Fig. 1. Ion chamber construction.

channel (both X and Y directions) by means of the 8 channel analog multiplexers (AM3705C). The inputs to the X-axis multiplexers are from a resistor divider network, giving a uniform series of points across the CRO which correspond with the uniform spacing of the ion chambers. If nonuniform spacing of the ion chambers is used, then the X-axis display can be altered to correspond. The 2N3643 transistor and 741 add a small horizontal sweep to each spot on the screen, giving a series of lines as shown in Figure 6, *A* and *C*. The length of this sweep can be varied by means of the 5K preset potentiometer to obtain a series of lines or spots. This sweep signal is then added to the horizontal X display signal in the 741 operational amplifier shown at the top of Figure 3.

The ion chamber outputs are sequentially sampled by the AM3705C analog multiplexers as shown in Figure 4, the output of which passes to a 741, where a D.C. voltage (preset) corresponding to the approximate mean amplifier signal can be subtracted if displayed on a D.C. CRO. The A.C. position is used for adjusting the offset voltages of each of the amplifiers. The 16 pole changeover switch (range control) enables the flatness checker to be used on a Metropolitan Vickers Series I Linac (4 MV) with an output of 150 r/minute, and also on a Toshiba LMR13B (10 MV) with an output of about 350 r/minute.

The 2 Kohm potential dividers which perform the range function are preset initially to the required voltage ratio which is determined by the Linac x-ray output ratio. The 10 Kohm resistor and AAZ18 diode protect the AM3705C from voltages greater than 5.3 volts which could occur if the gain switch was in the wrong position for a high dose rate.

Figure 5 shows the −200 volt regulated high tension supply for the ion chambers. The relay and its associated 741 circuitry stop the full H.T. from being suddenly applied to the ion chambers, which could possibly damage the MOSFET input stages of the amplifiers.

Figure 6, *A* and *B* shows identical outputs from the Toshiba LMR13B displayed

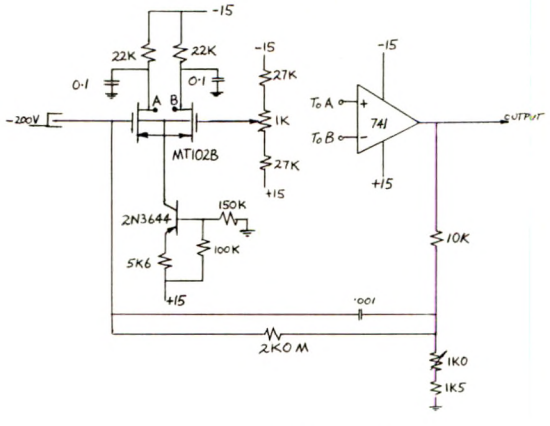


Fig. 2. Ion chamber amplifiers.

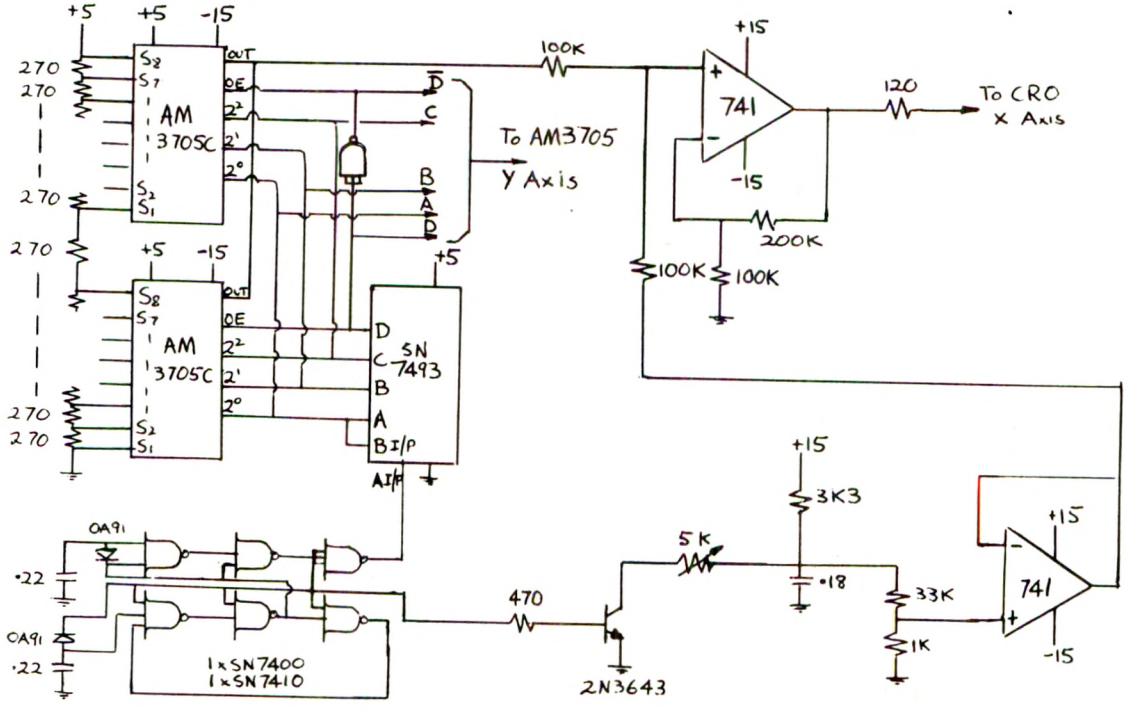


FIG. 3. X axis display.

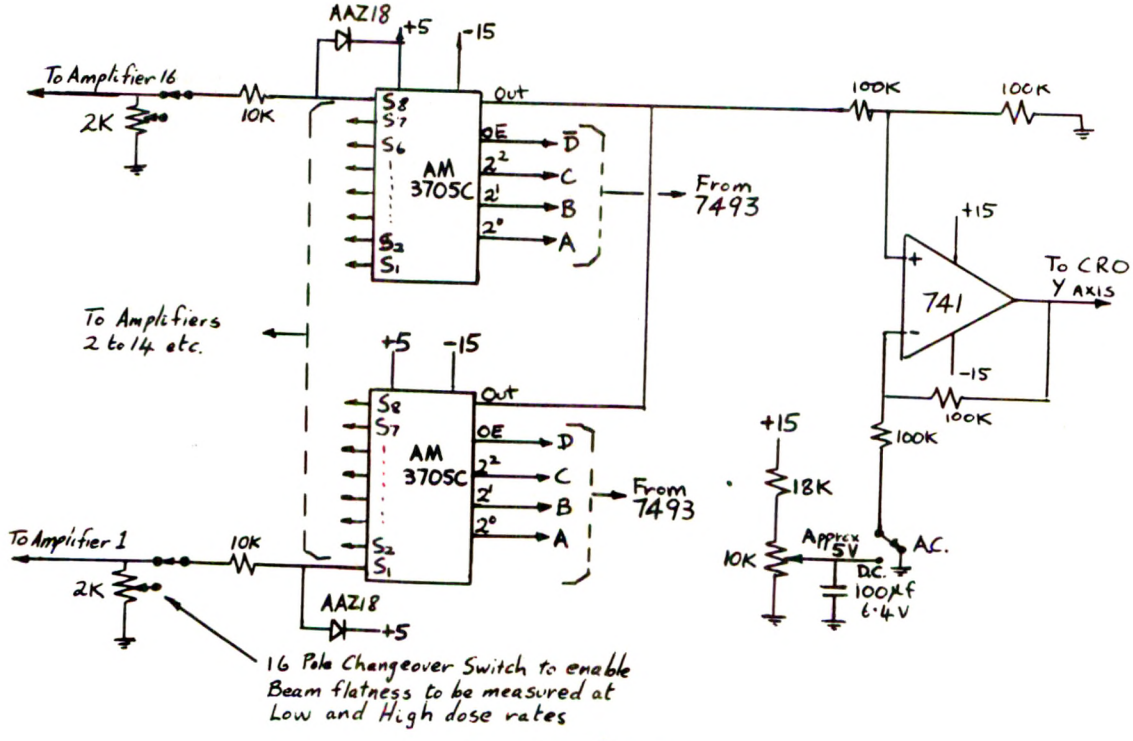


FIG. 4. Y axis display.

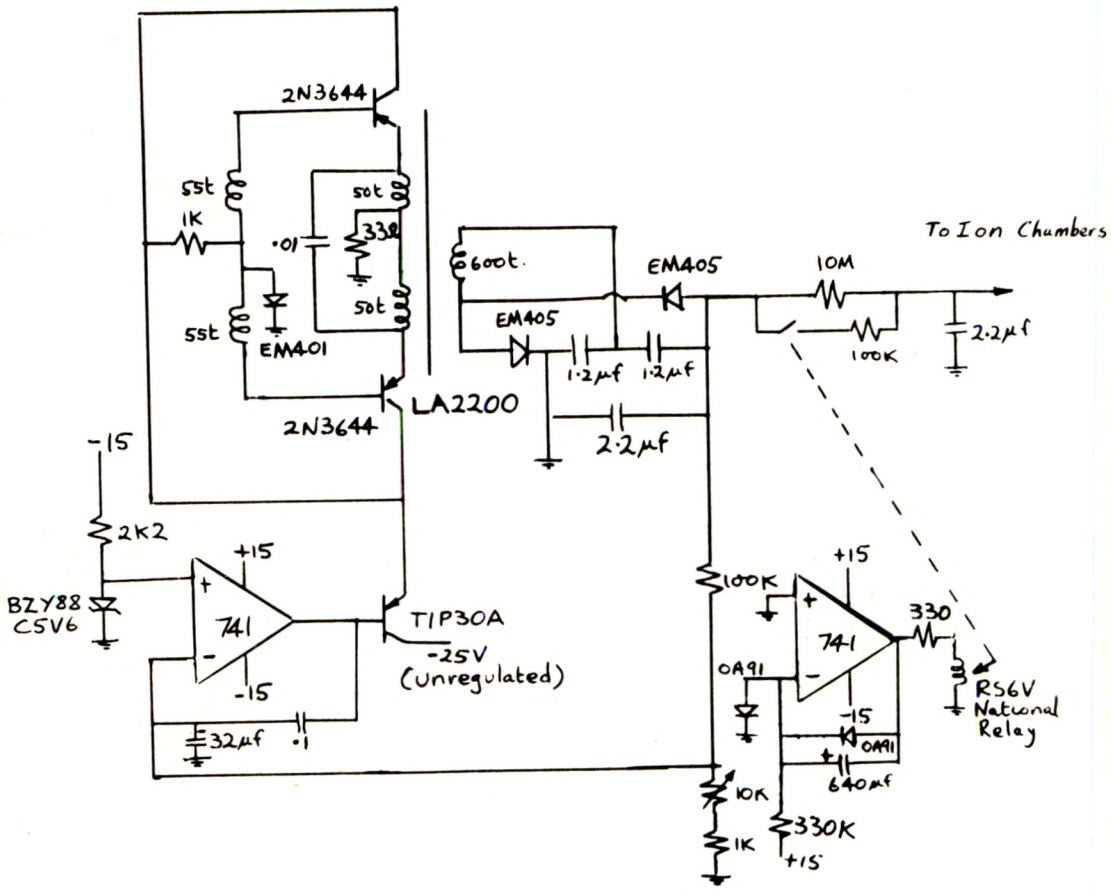
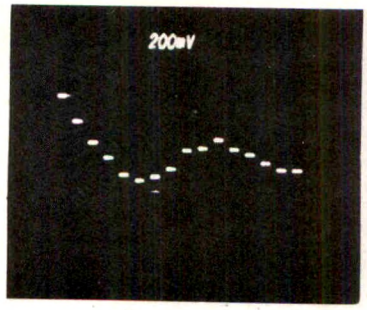


Fig. 5. High tension supply.

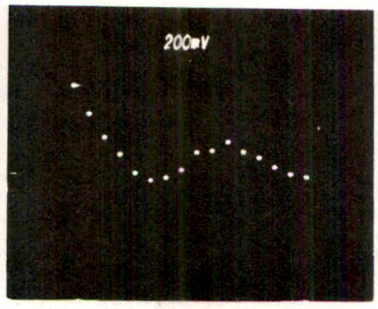
as either lines or dots, and Figure 6*C* shows the flattened beam output of this linac.

Figure 6*D* shows the beam flatness of the Metropolitan Vickers Series I Linac, while Figure 6*E* shows the beam output with the flattening filter removed. In both these latter cases, the detectors at the extremities are only partially in the beam because of the positioning of the monitor. A photograph of the flatness monitor attached to the LMR13B is shown in Figure 7. The transformer for the monitor is mounted in the Linac and the output leads pass through the Linac and on to the control room where the signals are displayed on the CRO. Calibration of the ion chambers and amplifiers was achieved by mechanically moving the monitor through the beam of a Picker (C 1000) cobalt 60 treatment machine, setting each ion chamber in turn at the center of the beam. Alternatively, the monitor could be calibrated on a Linac if the above procedure for a cobalt 60 beam was repeated and a reference chamber was placed as near as possible to the center of the beam. The flatness monitor has been operating satisfactorily for over a year now, and has proved an invaluable asset in the daily checking of the Linac beam flatness.

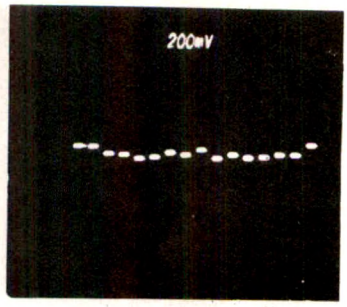
Many simple variations of this equipment are possible, such as adding a set of chambers at 90° to check the beam flatness in both of the adjustable directions simultaneously, the outputs being displayed on a double beam CRO. The monitor could be motorized, so that it could be remotely con-



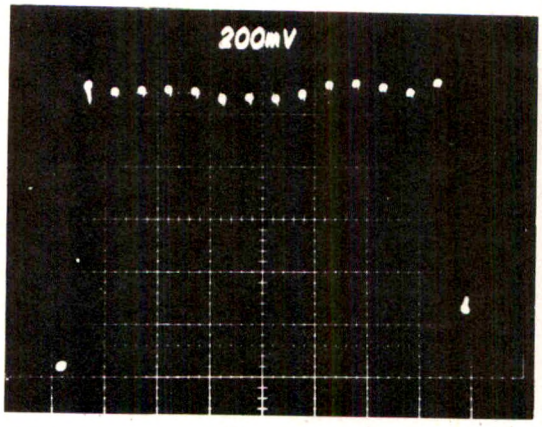
A



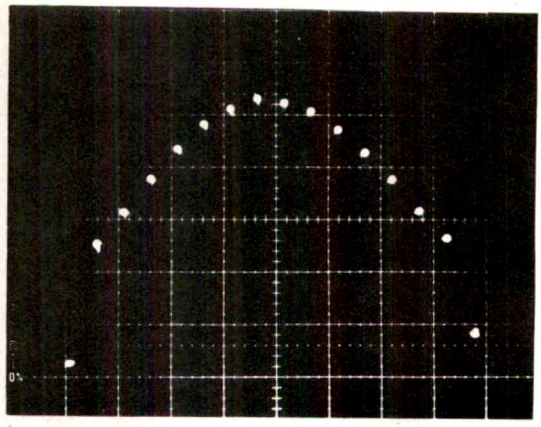
B



C



D



E

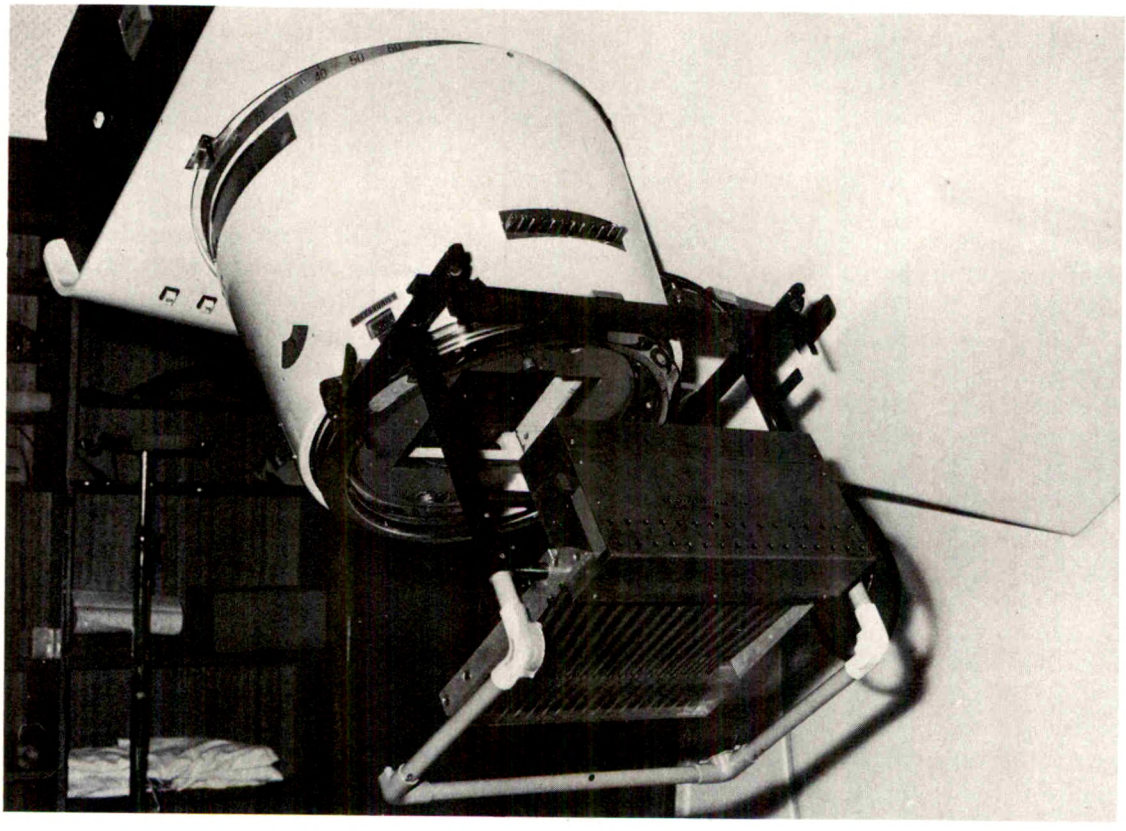


Fig. 6. (*A–E*) Typical output displays.

trolled to rotate ±180° about the beam axis. If the frequency of the oscillator which controls the sampling rate is reduced (or pulses produced manually) an X−Y recorder can be connected instead of a CRO to give a permanent record of beam flatness.

With graphite chambers etc., the monitor could be permanently sited in the head of the Linac, giving a continuous monitoring of beam flatness during patient treatments.

SUMMARY

A beam flatness monitor is described which consists of 16 ion chambers and amplifiers, the outputs of which are sequentially sampled and displayed as a series of dots or lines on a conventional CRO, giving an instantaneous display of beam flatness variations.

The device is used routinely for checking the beam flatness of our Linacs.

The device involves no new principles, but represents a radical change in approach to the checking of Linac beam uniformity.

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Fig. 7. Complete monitor.

AN INSTRUMENT FOR THE RAPID CHECK OF OUTPUT, ENERGY AND FIELD SYMMETRY OF SUPERVOLTAGE THERAPY EQUIPMENT*

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THERE is a definite requirement to continuously monitor the operating characteristics of radiation therapy machines. The instances where isotopic teletherapy units have deviated from an output calculated by the known decay rate of the isotope are relatively rare. However, linear accelerators and similar machines which depend on the calibration of a monitor ionization chamber must be suspect as to the accuracy of output calibration and should be checked frequently, preferably at the beginning and end of a treatment session by the therapy technician. Commercially available dosimeters are not particularly well suited to this purpose, being cumbersome to set up and requiring some skill in their operation.

INSTRUMENTATION

An instrument developed to measure the output, energy and beam symmetry is shown in Figure 1. It consists of a block of iron bark wood, 13×13×22 cm. After a suitable seasoning period, the surface is sealed by clear varnish. The specific gravity of the blocks used was 1.08. A thin white polystyrene plate is affixed to the top sur-

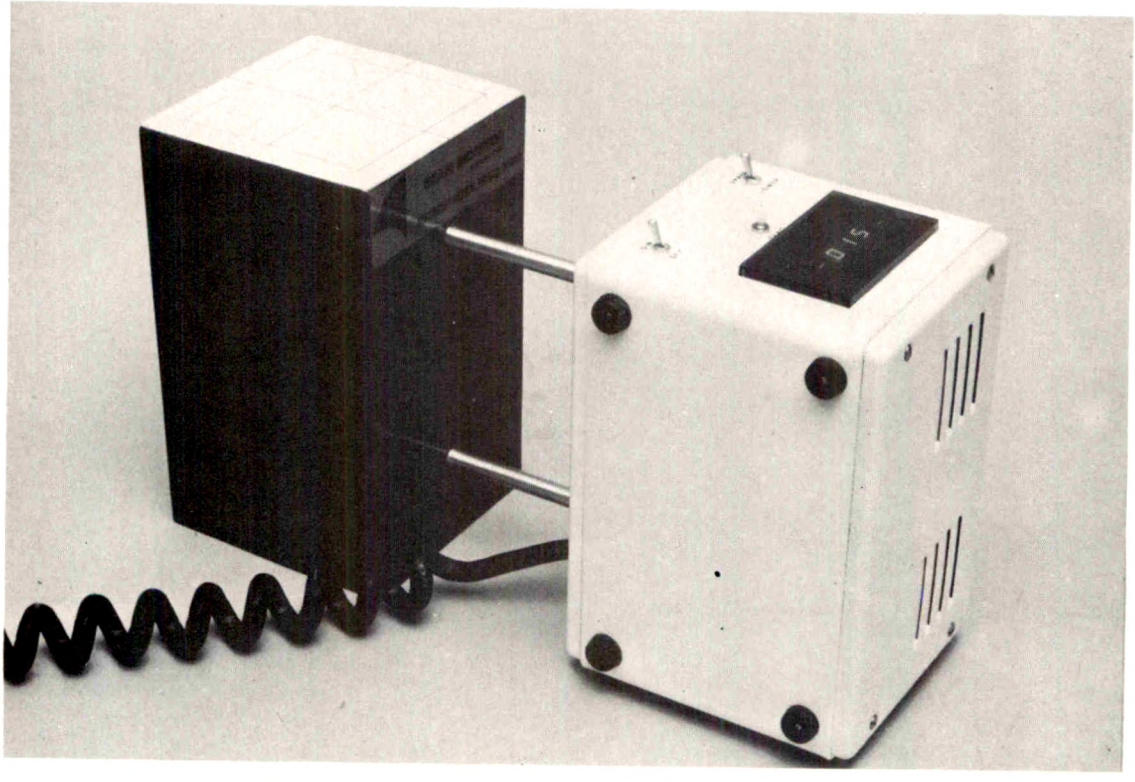

FIG. 1. The beam monitor.

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face with a 10 cm. square and center lines marked. Two silicon diode radiation detectors are located down the central axis of the block at 5 and 17 cm. depth. The shield of the coaxial cable connecting the diodes to the amplifiers is brought around the diodes to make contact on the distal side. This serves to reduce to negligible levels radio frequency pick-up and further will serve to reduce the photon energy dependence of the diodes.[1] The diodes employed in each device are selected for high sensitivity and grouped in pairs of comparable sensitivity. No attempt is made to adjust the gain of each channel to obtain equal response. The design criteria for the sensitivity of the instrument are that the reading should exceed 100 digits for a given dose of 200 rads.

The circuit employed is shown schematically in Figure 2. The output of each diode is fed to a separate amplifier where the signal is integrated. After the radiation exposure, the charge delivered by each diode is available for display on a digital panel meter selected by the switch S_1. The instrument is returned to zero by the switch S_2. The input impedance of the chopper stabilized operational amplifiers used is defined by the input resistor. A 2.7 Kohm resistor was selected to give sufficient sensitivity and minimal dose rate dependence of the response. The current generated in the absence of radiation, which has been investigated recently by Petushkov and Parker,[6] is balanced out at the input of the amplifier. The temperature variations that exist in the environment for which the instrument was designed, namely a radiation therapy department, have not resulted in

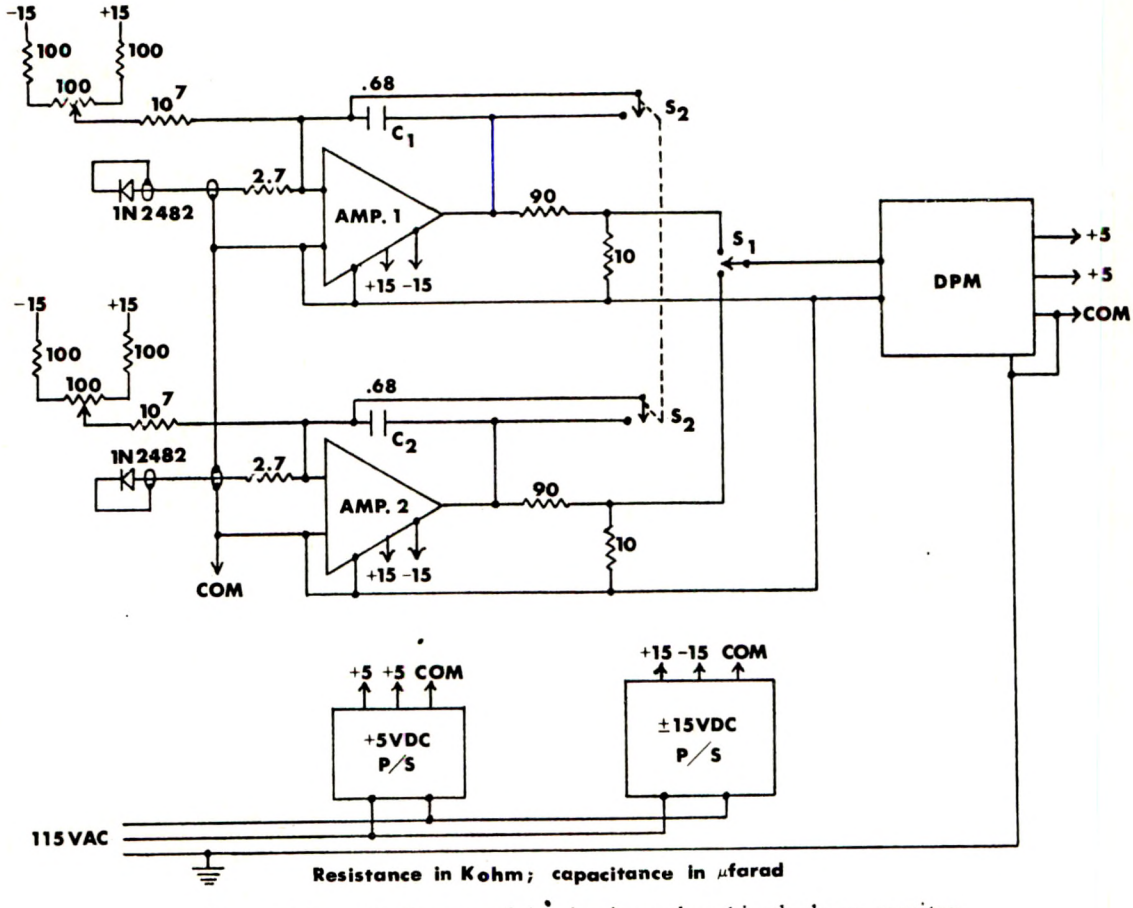

Fig. 2. Schematic diagram of the circuit employed in the beam monitor.

TABLE I

THE RATIO OF THE UPPER TO LOWER DIODE READING AS A FUNCTION OF ENERGY, NORMALIZED TO COBALT 60

Source	Effective Energy, MeV	Calculated for 10×10 Field: Dose at 5 cm. Depth / Dose at 17 cm. Depth	Measured: Upper Diode Reading / Lower Diode Reading
2 MV x rays	0.73	1.11	1.14
Cobalt 60	1.20	1.00	1.00
4 MV x rays	1.50	0.90	0.89
8 MV x rays	2.70	0.79	0.83

deterioration of the zero drift greater than the 1 digit per minute design specification. A large temperature excursion results in a rapid change of the digital display which would make the instrument unusable, and would not give a false stable reading.

The instrument was designed to monitor supervoltage machines operating in the range 2–10 MV x rays. In accord with ICRU recommendations,[3] the upper diode, which is intended primarily to monitor output, is located at 5 cm. depth. The location of the lower diode was determined by maintaining a separation of the diodes which would allow a symmetry check in a 30×30 cm. field. A depth of 17 cm. was selected. The expected ratio of upper to lower diode reading calculated from published[2] tissue-air ratio and tissue maximum ratio Tables has been compared with that measured and is shown in Table 1. The discrepancy between the measured and calculated ratios may be ascribed to changes in the photon spectrum with depth and consequent variations in the diode response per tissue rad.

The precision of the instrument was determined by exposing the device in a beam of cobalt 60 gamma radiation twice a day over a period of 46 days when 58 individual readings were obtained. These results are shown in Table II.

TABLE II

PRECISION OF 58 MEASUREMENTS ON A COBALT 60 TELETHERAPY UNIT. THE READINGS ARE CORRECTED FOR THE DECAY OF THE COBALT 60 SOURCE OVER A 46 DAY PERIOD

	Average	Standard Deviation	Standard Error
Upper	410.3	2.40 (0.6 per cent)	0.45
Lower	178.7	1.60 (0.9 per cent)	0.31
Ratio	2.296	0.01 (0.4 per cent)	—o—

RESULTS

The reproducibility of the set-up in these measurements, which were made at 60 cm. SSD,* was no better than ±2 mm., which would introduce a maximum variation in the dose delivered from day to day on the order of 0.6 per cent. This is reflected in the fact that the precision of the ratio measurement was better than the individual measurements, since the ratio would be relatively unaffected by small variations in SSD.

The long-term stability of the system was investigated by monitoring the output of an 8 MV linear accelerator over a 10 month period. The sensitivity of the instrument was measured intermittently during this period using a calibrated cobalt 60 beam. The instrument was purposely heavily irradiated on each occasion during the warming up of the machine, when it was estimated that a minimum dose of 4,000 rads was delivered each day to the instrument. The results are shown in Figure 3. Radiation damage is apparent and is of the same order as that reported by Parker and Morley.[5] It would be expected that the Frenkel defects thought to be responsible for radiation damage would anneal to some extent at room temperature so that at lower dose rates the radiation damage would be no greater than

* Source-skin distance.

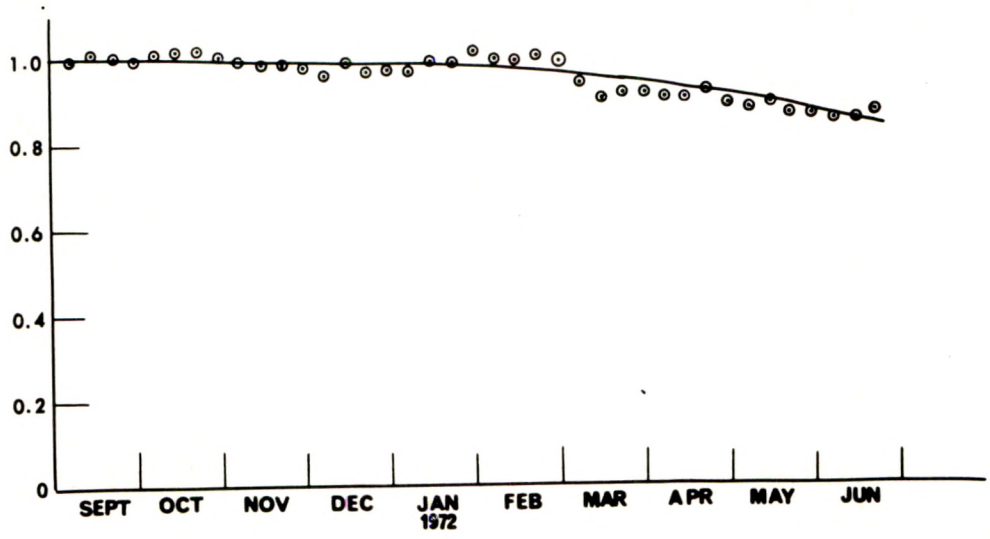

Fig. 3. Long-term response of upper diode. The data points are the mean of 5 consecutive daily readings. The exposure conditions were: 8 MV x rays, 200 rads given dose. The solid line represents the loss of sensitivity as measured in a calibrated cobalt 60 beam. Normalization has been made to the initial reading.

shown here. In normal use the instrument will receive a dose of about 400 rads per day which will result in a drop in sensitivity of 3 per cent in about 50 months which is considered acceptable.

DISCUSSION

The requirement to monitor the symmetry of the fields of linear accelerators has been reported by Naylor and Chiveralls[4] and Wright *et al.*[7] This is particularly relevant in a bent beam type of accelerator or one in which multiple modes are used when it must be assured that the flattening filter is brought into precise alignment. The variations produced by changing the bending

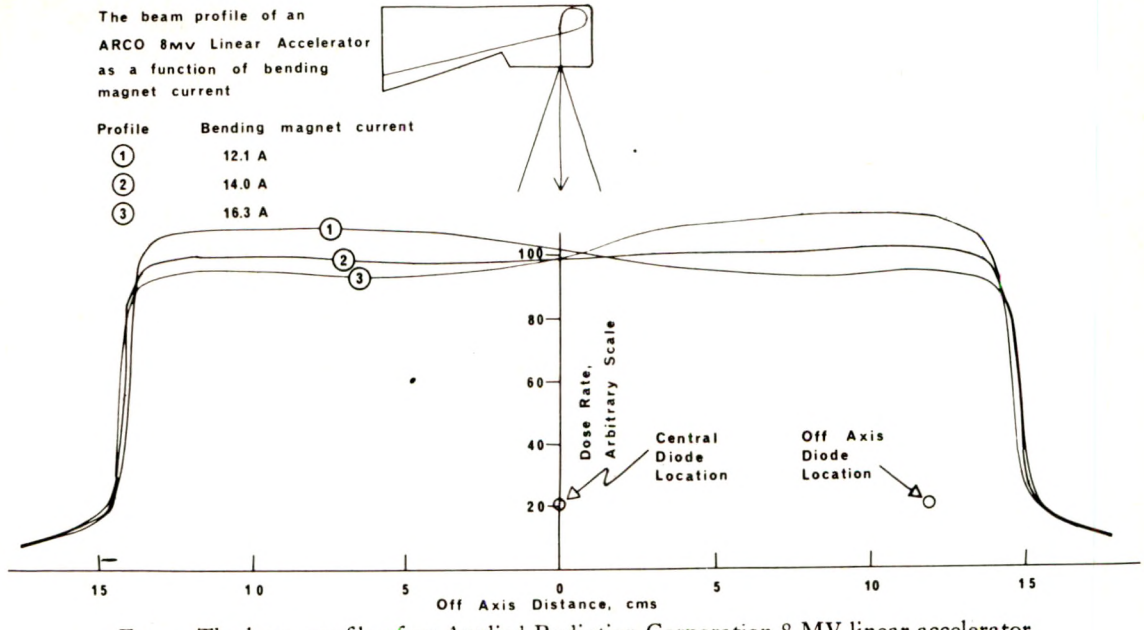

Fig. 4. The beam profile of an Applied Radiation Corporation 8 MV linear accelerator as a function of bending magnet current.

TABLE III

THE CHANGE IN BEAM SYMMETRY DETERMINED BY THE BEAM MONITOR AS A FUNCTION OF BENDING MAGNET CURRENT ON AN APPLIED RADIATION CORPORATION 8 MV LINEAR ACCELERATOR

Bending Magnet Current	Off Axis Diode Reading / Central Axis Diode Reading
12.1A	0.895
13.1	0.940
14.0	1.020
15.2	1.090
16.3	1.150

magnet current of an Applied Radiation Corporation Mevatron VIII linear accelerator are illustrated in Figure 4. The variations in the ratio of the reading of a diode located at 12 cm. off the central axis to that on the central axis are shown in Table III.

It should be stressed that we do not consider this instrument a basic calibration device, although it has been of use to make an over-all check on the original calibration and percentage depth dose measurements made on linear accelerators. Typically, the readings of the diodes obtained on five 4 MV linear accelerators have been predicted by measurements made in a calibrated cobalt 60 beam to better than 2 per cent.

SUMMARY

Seven of the described instruments have been produced and are in use at radiation therapy centers in Washington and Oregon. The device has already served its purpose to alert the radiotherapist to a malfunction in his machine on numerous occasions.

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Fifty-seventh Annual Meeting: Americana Hotel, San Juan, Puerto Rico, May 4–9, 1975.

EDITORIAL

FIFTY-SEVENTH ANNUAL MEETING OF THE AMERICAN RADIUM SOCIETY

THE Americana Hotel in San Juan, Puerto Rico has been chosen by the Executive Committee of the American Radium Society as the meeting site for the Fifty-Seventh Annual Scientific Convention which will take place May 4 to 9, 1975. Members and guests who attended the 1960 annual meeting in San Juan will remember the pleasant climate, the variety of the Island's beautiful tropical scenery, its Spanish heritage, and the diversified daytime activities and night life.

Puerto Rico, a Commonwealth voluntarily associated with the United States, retains its Spanish culture and traditions. Spanish is the main language but English, the second language, is understood and spoken throughout the Island. San Juan, the oldest city under the American flag, is a modern metropolis which offers its visitors a variety of experiences. Its old section has been maintained as it was centuries ago, but the city also has modern hotels with luxurious facilities, casinos, good restaurants, and excellent entertainment featuring top names in international show business.

The scientific program which is far advanced in preparation, conforms to the multidisciplinary objectives of the American Radium Society, the oldest clinical oncologic society in the U.S.A. Scientific sessions will be held in the mornings, Monday through Friday from 9:00 A.M. to 1:00 P.M. Afternoons will be free for informal meetings and personal contacts, or for sports, sight-seeing, recreation, or rest.

This meeting qualifies for Category I credit towards the Certificate in Continuing Medical Education of the A.M.A.

The traditional Janeway Lecture will be delivered by Dr. George Lewis, Jefferson Medical University in Philadelphia. He has chosen the subject: "Ovarian Cancer: Multifacet Disease; Multifarious Therapy and Therapists." The most outstanding paper submitted by a resident will receive an award and will form part of the program. Symposia on the following subjects have been organized: *The Role of Radiation Therapy in the Management of Early Breast Cancer; Multidisciplinary Approach to the Management of* T_3 *and* T_4 *Head and Neck Tumors; Status of Interstitial Curietherapy in Present Cancer Therapy; Prevention of Metastases;* and *Treatment of Carcinoma of Endometrium.*

The Americana Hotel, in close proximity to the San Juan International Airport, which has direct flights to and from most of the major cities in the nation, is efficiently operated by American Airlines and is located in famous Isla Verde Beach. Facilities for swimming, skin diving, tennis, golf, sailing, and deep sea fishing are available at the hotel or in the nearby vicinity.

The Arrangements Committee, under Dr. Luis Vallecillo, Puerto Rico's leading cancer surgeon, is preparing a very active social program which will include cocktail parties, a mid-week afternoon party in a tropical setting, a banquet-dance, and an attractive series of social activities for the ladies.

Registration is open to all interested physicians. In particular, we welcome the members of the cancer team which includes: basic researchers, surgeons, diagnostic radiologists, chemotherapists, pathologists, immunologists, radiotherapists, gynecologists,

nuclear medicine specialists, physicists, etc.

The young doctors will be happy to know that federal grants cover transportation expenses to Puerto Rico and that the negotiated hotel rates are $31/double, plus tax and service charge.

No registration fee will be charged to members and residents adequately supported by a letter from the training program director. Non-member guests will be charged a registration fee.

Members and non-members are encouraged to register in advance to facilitate their arrival procedure. There will be no official travel agent for this meeting. Each person will be free to make his own travel arrangements. Hotel reservations may be made by writing to Mr. Edward Rodas, Reservation Manager, Americana Hotel, P.O. Box 5628, San Juan, Puerto Rico 00905.

For information on the meeting you may write to Dr. Luis Vallecillo, Chairman of Arrangements Committee, American Radium Society 1975 Meeting, c/o Puerto Rico Nuclear Center, San Juan, Puerto Rico 00935.

We look forward to seeing our friends and making new acquaintances during the American Radium Society Meeting in San Juan in May 1975.

Victor A. Marcial, M.D.
President
American Radium Society

NEWS ITEMS

WINTER MEETING OF MINNESOTA RADIOLOGICAL SOCIETY

The First K. W. Stenstrom Memorial Lecture will be given by Leo G. Rigler, M.D., Professor and Chairman Emeritus, Department of Radiology, University of Minnesota, Professor of Radiology, Department of Radiological Sciences, University of California, Los Angeles, February 1, 1975 at the Minnesota Club, St. Paul, Minnesota at 8:00 P.M.

The title of the Lecture is: "A Successful Academic Partnership: K. Wilhelm Stenstrom and the Department of Radiology of the University of Minnesota."

THIRD ANNUAL DIAGNOSTIC RADIOLOGY SEMINARS

Club Mediterranée, Tahiti

These seminars will be held at the famed Club Mediterranée in Tahiti, February 21–March 1, 1975, immediately following the UCSF Diagnostic Radiology Postgraduate Course. Ample time will be provided to enjoy the resort sports and activities of this beautiful island.

This meeting qualifies for Category 2 credit towards the certificate in Continuing Medical Education (Physicians Recognition Award), on an hour for hour basis.

Daily seminars will consist of small group discussions concerning problems in Diagnostic Radiology encountered by the clinical radiologist. Registrants will rotate through the various subspecialties and will receive tutorial instruction based upon illustrative roentgenograms.

The Guest Faculty consists of Drs. Charles A. Gooding, Thomas H. Newton, Alphonse J. Palubinskas, and Stewart R. Reuter.

For mail application please write to: Diagnostic Radiology Seminars, 200 South Ridgewood Road, Kentfield, California 94904.

FOUR DAY ONCOLOGY SEMINAR SET BY UCLA EXTENSION

The multidisciplinary approach to the management of solid neoplasms will be stressed at "The Third Annual UCLA Seminar on Modern Concepts in Oncology" offered by UCLA Extension and the UCLA School of Medicine, Thursday, February 27, to Sunday, March 2, at the Beverly Hilton Hotel in Beverly Hills, California.

The four day seminar will emphasize the interrelationship between therapeutic modalities—surgery, radiation therapy, chemotherapy or immunotherapy—in planning optimum cancer therapy.

Co-sponsored by the Division of Oncology of the Department of Surgery, the program is of interest to the well trained general physician and surgeon as well as the medical oncologist and radiation therapist.

General topics for discussion will include "Immunology and Immunotherapy," "General Concepts," "Breast Cancer—Management of Primary Disease," "Breast Cancer: Management of Advanced Disease," "Colorectal Neoplasms," "Melanoma," "Sarcomas," "Biliary Pancreatic Neoplasms" and "Hepatic Neoplasms: Primary and Metastatic."

Course chairman is Donald L. Morton, M.D., Professor of Surgery and Chief of the Division of Oncology at the School of Medicine.

The Guest faculty includes: Tapas Das Gupta, M.D., Professor and Chief, Division of Surgical Oncology, University of Illinois School of Medicine, Chicago; Vincent T. De Vita, Jr., M.D., Director, Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Bethesda, Maryland; Thomas Hall, M.D., Associate Director, Comprehensive Cancer Center, University of Southern California School of Medicine, Los Angeles; James Holland, M.D., Professor and Chairman, Department of Oncology, Mount Sinai Hospital School of Medicine, New York, New York; Morton M. Kligerman, M.D., University of New Mexico School of Medicine, Albuquerque, New Mexico; and Robert Lindberg, M.D., University of Texas at

Houston, M.D. Anderson Hospital and Tumor Institute, Houston, Texas.

Further information is available by writing P.O. Box 24902, Department of Continuing Education in Health Sciences, University Extension, UCLA, Los Angeles, California 90024.

INTERNATIONAL ACADEMY OF PATHOLOGY

U.S.-Canadian Division

The 64th Annual Meeting will be held at the Marriott Hotel in New Orleans, Louisiana, from Tuesday evening March 4 through Saturday March 8, 1975.

The annual Maude Abbott Lecture titled "Pathology and Preventive Medicine" will be delivered on Wednesday March 5 by Dr. John Higginson, Director, International Agency for Research on Cancer, Lyon, France.

Further information about the meeting may be obtained from Dr. Leland D. Stoddard, Secretary-Treasurer, U.S.-Canadian Division, International Academy of Pathology, Department of Pathology, Medical College of Georgia, Augusta, Georgia 30902.

Information about Short Courses, the EM Course to be given Friday March 7 and Saturday March 8, 1975, and the Long Course may be obtained from Mrs. J. Preston, IAP Registrar, Armed Forces Institute of Pathology, Room 4090, Washington, D. C. 20306.

COURSE ON DISEASES OF BONES AND JOINTS

International Academy of Pathology

A comprehensive program on Diseases of Bones and Joints will be given by a Faculty of 16 authorities at the Annual Meeting of the U.S.-Canadian Division of the International Academy of Pathology in New Orleans, Louisiana. The course will be given at the Marriott Hotel, Thursday, March 6, 1975.

Course Directors are: Dr. Lauren V. Ackerman, Professor of Pathology, State University of New York, Stony Brook, New York and Dr. Harlan J. Spjut, Professor of Pathology, Baylor College of Medicine and Pathologist, St. Luke's Episcopal Hospital, Texas Medical Center, Houston, Texas.

Further information may be obtained from Mrs. J. Preston, IAP Registrar, Armed Forces Institute of Pathology, Room 4090, Washington, D. C. 20306.

DIAGNOSTIC ONCOLOGIC RADIOLOGY

Current Concepts in Cancer Diagnosis

This course will be held at the Sheraton-Boston Hotel, Boston, Massachusetts, March 20–22, 1975.

The Course Directors are: Ernest J. Ferris, M.D., Chief, Department of Diagnostic Radiology, University Hospital, Professor of Radiology, Boston University School of Medicine and Jerome H. Shapiro, M.D., Director, Department of Radiology, Boston University Medical Center, Professor and Chairman, Boston University School of Medicine.

This course will correlate some clinical and pathologic problems in neoplasia with radiology. The main emphasis will be on the current concepts in diagnostic radiology. Newer modalities as well as the use of conventional and correlative new special procedure examinations will be stressed.

The faculty will be from Boston University Medical Center and other outstanding physicians from around the country. There will not be an attempt to cover every aspect of diagnostic oncologic radiology, but there will be some emphasis on the pancreas, adrenals, liver, kidney, retroperitoneal soft tissue tumors, lung, mediastinum, bone, breast, and the lymphomas.

A distinguished Guest Faculty will participate in the program.

For further information please contact: Dr. Daniel S. Bernstein, Boston University Medical Center, 720 Harrison Avenue, Suite 206, Boston, Massachusetts 02118.

WORKSHOP ON RECONSTRUCTIVE TOMOGRAPHY IN RADIOLOGY AND NUCLEAR MEDICINE

This Workshop sponsored by The Ed-

ward Mallinckrodt Institute of Radiology and Biomedical Computer Laboratory, Washington University School of Medicine, will be held in San Juan, Puerto Rico, April 17–19, 1975.

The workshop will provide a forum to mathematicians, physicists, engineers, and clinicians for in depth discussion of reconstructive tomography, in order to determine fruitful areas of research, development, and clinical applications.

Participants should have a working knowledge of reconstructive tomography. Registration is limited to 150.

For further information, please contact Michel M. Ter-Pogossian, Ph.D., Mallinckrodt Institute of Radiology, 510 South Kingshighway, St. Louis, Missouri 63110.

SYMPOSIUM ON POLYTOMOGRAPHY OF THE TEMPORAL BONE

The 11th two day Symposium on Polytomography of the Temporal Bone will be given under the auspices of The Wright Institute of Otology at Community Hospital, Indianapolis, Indiana on April 26 and 27, 1975.

Subjects covered are: "Basic Anatomy of the Temporal Bone" and "Technique of Polytomography of the Temporal Bone" with demonstrations of normal tomograms. Pathological conditions revealed by polytomography, such as cholesteatoma, ossicular chain problems, otosclerosis, fractures, foreign bodies, tumors, and congenital anomalies are shown on original tomograms and the clinical applications discussed.

Number of registrants is limited to 18.

Inquiries should be directed to: The Wright Institute of Otology, Inc., Community Hospital of Indianapolis, Inc., 1500 North Ritter Avenue, Indianapolis, Indiana 46219.

NATIONAL CONFERENCE ON ADVANCES IN CANCER MANAGEMENT

Part II: Detection and Diagnosis

The American Cancer Society—National Cancer Institute sponsors this conference which will be given at the Denver Hilton Hotel, Denver, Colorado, May 1–3, 1975.

The stated purpose of this conference is as follows: "Progress in the identification of groups at high-risk for cancer, improvement in diagnostic techniques and equipment and an increased research effort in these areas serves as the basis for this conference. Presentations by experts in the many disciplines involved will provide information that should improve the ability of the practicing physician to detect and diagnose cancer earlier and with greater accuracy."

Sessions are open to all members and students of the medical and dental professions. Advance registration is requested. There is no registration fee.

Accredited by the American Medical Association and the American Academy of Family Physicians.

For further information please write: Sidney L. Arje, M.D., American Cancer Society, 219 East 42nd Street, New York, New York 10017.

SYMPOSIUM ON HEAD AND NECK CANCER

"Symposium on Head and Neck Cancer" will be held May 21, 1975, on the campus of the University of Pittsburgh from 9:15 A.M. to 3:40 P.M.

The program is sponsored by the University of Pittsburgh Schools of Dental Medicine and Medicine (University Health Center of Pittsburgh), the Allegheny County Unit of the American Cancer Society, and the Pittsburgh Chapter of the International Association for Dental Research.

"Symposium on Head and Neck Cancer" is acceptable for $4\frac{1}{2}$ credit hours in Category 1 for the Physician's Recognition Award of the American Medical Association.

For further information please contact: William M. Cooper, M.D., Division of Continuing Education, University of Pittsburgh School of Medicine, 1022-H Scaife Hall, Pittsburgh, Pennsylvania 15261.

BOOK REVIEW

Clinical Pediatric Oncology. Edited by Wataru W. Sutow, M.D., Pediatrician and Professor of Pediatrics, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, Houston, Texas; Teresa J. Vietti, M.D., Professor of Pediatrics, Mallinckrodt Department of Pediatrics, Washington University School of Medicine; Associate Pediatrician, Barnes and Associated Hospitals; Director, Division of Hematology and Oncology, St. Louis Children's Hospital, St. Louis, Mo.; and Donald J. Fernbach, M.D., Professor of Pediatrics, Baylor College of Medicine; Chief, Hematology and Oncology Service at Texas Children's Hospital; Director, Research Hematology Laboratory, Texas Children's Hospital, Houston, Texas. Cloth. Pp. 602, with 216 illustrations. Price, $35.50. C. V. Mosby Company, Publishers, 11830 Westline Industrial Drive, St. Louis, Mo. 63141, 1973.

This book is a synthesis of interest and experience of investigators and consultants who comprise the Pediatric Division of the Southwest Cancer Chemotherapy Study Group.

The book, edited by 3 well-known authorities, is composed of 28 chapters from 36 contributors and contains 216 illustrations and many useful tables. The editors have aimed the book at the clinician, so that there is a greater emphasis on clinical aspects of the various diseases than upon the histopathology. The overall coherence of the book is remarkably good considering the multi-authorship. The arrangement of the chapters from the general aspects of care of the child with cancer to that of detailed discussions of major disease entities although arbitrary, is quite acceptable. Emphasis is made upon the steady improvement in the over-all survival rate in children with cancer much to the credit of the multidisciplinary approach that integrates the talents of the clinical oncologist, radiotherapist, and surgeon. The book is a success in its major objective of reviewing the status of cancer in children and aquainting the reader with current progress.

Chapters 1 through 8 cover general aspects, etiology, general surgical considerations, basic concepts and clinical implications of radiation therapy, the conceptual basis and general aspects of chemotherapy and principles of total care: physiologic and psychologic support. The concept of the period of risk[1] is discussed and its general validity emphasized for solid tumors. Those factors of childhood tumors and relationships to congenital malformation are mentioned, particularly in the younger child.[4] Chapter 4 covering the basic concepts of radiation therapy gives a good outline of treatment planning as well as factors affecting biologic effects of ionizing radiation. General aspects of chemotherapy are outlined in Chapters 5 and 6. The importance of sensitive and sophisticated diagnostic procedures is emphasized, particularly lymphangiography, angiography, xerography, isotopic scanning, electron microscopy and tissue culture techniques.

Chapter 10 covering the management of acute leukemia excellently outlines the classification of leukemia and summarizes the remission induction with single and multiple patients. Chapter 11 covers extramedullary leukemia and emphasizes the high percentage of genitourinary tract involvement, 66 per cent in autopsy series.

Roentgenographic contribution to diagnosis in Hodgkin's disease is emphasized in Chapter 13. The chest examination is mandatory including tomography and oblique views. The lymphangiogram is a major advantage in diagnosis of retroperitoneal nodal disease, although the lymphangiogram does not visualize the high para-aortic nodes—an area likely to be involved, and consequently inferior venacavography can play a role for that area. The excretory urogram may also give indirect evidence of paraaortic nodal disease. Figure 13-11 gives a good schematic demonstration of staging classification and staging celiotomy is advocated. The non-Hodgkin's lymphoma of childhood is just as completely covered including a very thorough description of diagnostic aids; roentgenologic examinations employed being chest, excretory urography, lymphangiography and skeletal survey.

In Chapter 15 there is a detailed coverage of histiocytosis including a summary of historical

[1] Collins, V. P., Loeffler, R. K., and Tivey, H. Observations on growth rates of human tumors. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., 1956, *76*, 988–1000.

aspects and a focus on complications.

Chapter 16 is concerned with Wilms' tumor, the most common intra-abdominal tumor of childhood, and the associated congenital anomalies such as hemihypertrophy and aniridia are mentioned. Clinical staging and complications of therapy are discussed including post-irradiation bone changes. No mention, however, is made of the damage that is postulated to occur to muscle cells in irradiated young infants which probably plays a role in development of scoliosis.[2] Additionally there may be a worsening of scoliosis when these patients go into adolescence.[5] Neuroblastoma is the topic of Chapter 17, this being the most common malignant solid tumor of childhood. It is a well prepared chapter, but does not mention the apparent better survival rate of the extra-adrenal neuroblastoma *versus* the adrenal neuroblastoma, a phenomenon which has had recent emphasis in the literature.[3] Other chapters on specific tumors are well done and in particular Chapter 19 concerning malignant tumors of the central nervous system and Chapter 21 concerning primary malignant tumors of bone. The tables in this chapter are very useful, although there is a lack of emphasis of the contribution made by roentgenology to the diagnosis of these lesions.

Over-all this is an excellent compilation of the current status of clinical pediatric oncology which admirably emphasizes the multidisciplinary approach as the authors intended. Overlapping of material because of the multi-authorship is in no way cumbersome and probably contributes to the learning process for those who read the book through. The usefulness will even be greater as a reference source for current advances.—Lionel W. Young, M.D.

[2] Dawson, W. B. Growth impairment following radiotherapy in childhood. *Clin. Radiol.*, 1968, *19*, 241–256.

[3] Kelly, F. Prognosis in extra-abdominal neuroblastoma. *Acta radiol.* (Ther.), 1967, *6*, 100–104.

[4] Miller, R. W. Relation between cancer and congenital defects: epidemiologic evaluation. *J. Nat. Cancer Inst.*, 1968, *40*, 1079–1085.

[5] Young, L. W., Rubin, P., and Hanson, R. E. Extra-adrenal neuroblastoma: high radiocurability and diagnostic accuracy. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., 1970, *108*, 75–91.

BOOKS RECEIVED

Bronchial Carcinoma. By Thomas W. Shields, M.D., Professor of Surgery, Northwestern University Medical School, Chicago, Ill.; Chief of Surgery, VA Research Hospital; Attending Surgeon, Northwestern Memorial Hospital, Chicago, Ill.; with Sections on Immunologic Features and Immunotherapy by Roy E. Ritts, Jr., M.D., Professor and Chairman, Department of Microbiology, Mayo Graduate School of Medicine, Rochester, Minn. Cloth. Pp. 181, with some figures. Price, $12.75. Charles C Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Ill. 62717, 1974.

Roentgenology of the Foot: Principles and Practice. By Frank Weinstein, D.P.M., F.A.C.F.R., Editor, The Canadian Podiatrist; Consulting Podiatrist, Alberta Hospital, Norwood, and Auxiliary Grandview Hospitals, Edmonton, Alberta, Canada; with a chapter on Therapeutic Radiology in Podiatry by Albert G. Kalin, D.P.M., F.A.C.F.R., Straith Memorial Hospital, Southfield, Mich. Cloth. Pp. 334, with many figures. Warren H. Green, Inc., Publishers, 10 South Brentwood Boulevard, St. Louis, Mo. 63105, 1974.

Physicians' Desk Reference for Radiology and Nuclear Medicine. Editorial Consultants: M. Donald Blaufox, M.D., Ph.D., Associate Professor of Radiology and Medicine, Albert Einstein College of Medicine; and Leonard M. Freeman, M.D., Associate Professor of Radiology, Albert Einstein College of Medicine. Cloth. Pp. 407. Price, $8.50. Medical Economics Co., Box 58, Oradell, N. J. 07649, 1974.

A Practitioner's Guide to the Diagnostic X-Ray Equipment Standard. Paper. Pp. 11. Single free copies are available from the Bureau of Radiological Health (HFX-25), 5600 Fishers Lane, Rockville, Md. 20852, 1974.

Bone Dysplasias: An Atlas of Constitutional Disorders of Skeletal Development. By Jürgen W. Spranger, M.D., Universitäts-Kinderklinik, Mainz; Leonard O. Langer, Jr., M.D., University of Minnesota, Minneapolis; and H.-R. Wiedemann, M.D., Universitäts-Kinderklinik, Kiel. Cloth. Pp. 369, with 424 illustrations. Price, $48.00. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. 19105, 1974.

X-Ray Case Studies: 53 Cases Related to Diagnostic Radiology. By Florencio A. Hipona, M.D., Professor of Radiology, Boston City Hospital, Harvard Medical School; Lecturer in Medicine and Radiology, Boston University School of Medicine; Lecturer in Radiology, Tufts University School of Medicine; and Associate Director of Radiology, The Boston City Hospital, Boston, Mass.; with the assistance of Otoniel R. Sullesta, M.D., Instructor in Radiology, Harvard Medical School and Boston University School of Medicine; Associate in Radiology, The Boston City Hospital, Boston, Mass. Paper. Pp. 160, with many figures. Price, $10.00. Medical Examination Publishing Company, Inc., 65-36 Fresh Meadow Lane, Flushing, N. Y. 11365, 1974.

Pneumopelvigraphy in Modern Gynecological Diagnostics. By Giorgio Cittadini; in collabora-

tion with Giorgio Mallarini. Cloth. Pp. 248, with many figures. Price, $25.00. Piccin Medical Books, Via Porciglia 10, 35100 Padova, Italy, 1974.

Physical Mechanisms in Radiation Biology. Proceedings of a Conference held at Airlie, Va., Oct. 11–14, 1972. Sponsored by the U. S. Atomic Energy Commission, Division of Biomedical and Environmental Research. Edited by Raymond D. Cooper and Robert W. Wood. Paper. Pp. 326, with many figures. Price, $10.60. (CONF-721001.) National Technical Information Service, U. S. Department of Commerce, Springfield, Va. 22151, 1974.

Thérapeutiques non Mutilantes des Cancéreuses du Sein. Conservative Treatments of Breast Cancers. Symposium International, Strasbourg, Juin 1972. Secrétaire général: Pr Charles Gros. Paper. Pp. 425, with 183 figures. Price, 200 F. Masson et Cie, 120, Boulevard Saint-Germain, Paris-VI, France, 1974.

SOCIETY PROCEEDINGS

MEETINGS OF RADIOLOGICAL SOCIETIES*

UNITED STATES OF AMERICA

AMERICAN ROENTGEN RAY SOCIETY
Secretary, Dr. James Franklin Martin, 300 S. Hawthorne Rd., Winston Salem, N. C. 27103. Annual Meeting: Marriott Hotel, Atlanta, Ga., Sept. 30–Oct. 3, 1975.

AMERICAN RADIUM SOCIETY
Secretary, Richard H. Jesse, Dept. of Surgery, M. D. Anderson Hosp. and Tumor Institute, Houston, Tex. 77025. Annual Meeting: Americana Hotel, San Juan, Puerto Rico, May 4–9, 1975.

RADIOLOGICAL SOCIETY OF NORTH AMERICA
Secretary, Dr. Hillier L. Baker, Jr., Mayo Clinic, Rochester, Minn. 55901. Annual Meeting: Palmer House, Chicago, Ill., Dec. 1–6, 1974.

AMERICAN COLLEGE OF RADIOLOGY
Executive Director, William C. Stronach, 20 N. Wacker Drive, Chicago, Ill. 60606. Annual meeting: Portland-Hilton Hotel, Portland, Oregon, March 31–April 4, 1975.

SECTION ON RADIOLOGY, AMERICAN MEDICAL ASSOCIATION
Secretary, Dr. Antolin Raventos, Davis, Calif. Annual Meeting: Atlantic City, N. J., June 15–19, 1975.

AMERICAN BOARD OF RADIOLOGY
Secretary, Dr. C. Allen Good. Correspondence should be directed to Kahler East, Rochester, Minn. 55901.

Written Examination will be held in 14 selected sites, June 21, 1975.

Oral examinations will be held: Pittsburgh Hilton, Pittsburgh, Pa., June 2–7, 1975; Statler Hilton, Dallas, Texas, Dec. 8–13, 1975; Marriott Motor Hotel, Chicago, Ill., June 14–19, 1976; Sheraton Biltmore, Atlanta, Ga., Dec. 6–11, 1976.

Applications must be received in the Board Office before Sept. 30 of the year preceding the one in which the candidate wishes to be examined.

Deadline for filing applications for any examination in 1976 is September 30, 1975.

AMERICAN BOARD OF NUCLEAR MEDICINE, INC. A Conjoint Board of the American Boards of Internal Medicine, Pathology and Radiology and sponsored by the Society of Nuclear Medicine.

Application forms and further information are available from the American Board of Nuclear Medicine, 305 E. 45th St., New York, N. Y. 10017.

AMERICAN ASSOCIATION OF PHYSICISTS IN MEDICINE
Secretary, Kenneth D. Williams, M.S., Dept. Radiol., Washington Hospital Center, 110 Irving St., N.W., Washington, D.C. 20010. Annual Meeting.

AMERICAN SOCIETY OF THERAPEUTIC RADIOLOGISTS
Secretary, Dr. Robert W. Edland, 1836 South Ave., La Crosse, Wisc., 54601. Annual Meeting: San Francisco, California, Oct. 8–13, 1975.

AMERICAN NUCLEAR SOCIETY
Program Chairman, Werner K. Kern, IRD, Space Nuclear Systems, F 309, U. S. Atomic Energy Commission, Washington, D.C. 20545.

AMERICAN INSTITUTE OF ULTRASOUND IN MEDICINE
Secretary, John M. Reid, Ph.D., 556 18th Ave., Seattle, Wash. 98122. Annual Meeting.

AMERICAN SOCIETY OF NEURORADIOLOGY
Secretary, Dr. David O. Davis, Department of Radiology, 901 Twenty-third St., N.W., Washington, D. C. 20037. Annual Meeting.

FOURTEENTH INTERNATIONAL CONGRESS OF RADIOLOGY
Rio de Janeiro, Brazil in 1977.

INTERNATIONAL SOCIETY OF RADIOLOGY
Hon. Secretary-Treasurer, Prof. W. A. Fuchs, M.D., Department of Diagnostic Radiology, University Hospital, Inselspital, CH-3010 Bern, Switzerland.

ELEVENTH INTER-AMERICAN CONGRESS OF RADIOLOGY
Counselor for the United States, Dr. Juan A. del Regato, Univ. of South Florida, Tampa, Fla.
Secretary of Congress, Dr. Alberto Mejia, Apartado Aéreo 53737, Bogotá 2, Colombia. Meeting: Feb. 16–21, 1975.

INTER-AMERICAN COLLEGE OF RADIOLOGY
President, Dr. Miguel Dao y Dao, Apartado Postal 14213, Candelaria, Caracas, Venezuela, S.A.
Secretary of Congress: Dr. Alberto Mejia, Apartado Aereo 53737, Bogotá 2, Colombia, S.A. Meeting: Bogotá, Colombia, Feb. 16–21, 1975.

THIRD CONGRESS OF THE EUROPEAN ASSOCIATION OF RADIOLOGY
Secretary General, P.O. Box 14, 79 Lauriston Place, Edinburgh BHI IDB, Scotland, Meeting: June 22–27, 1975.

SECOND ASIAN AND OCEANIAN CONGRESS OF RADIOLOGY
Secretary, Dr. Buenaventura U. V. Angtuaco, Congress Secretariat Headquarters 2161 Taft Ave., Manila, Philippines.

Meeting: Manila, Philippines, Nov. 10–14, 1975.

ALABAMA CHAPTER OF ACR
Secretary-Treasurer, Dr. Lawrence E. Fetterman, 1720 Springhill Ave., Suite 201, Mobile, Ala. 36604. Meets time and place of Alabama State Medical Association.

ALASKA RADIOLOGICAL SOCIETY, CHAPTER ACR
Secretary-Treasurer, Dr. Maurice J. Coyle, 3200 Providence Ave., Anchorage, Alaska 99504.

AMERICAN OSTEOPATHIC COLLEGE OF RADIOLOGY
Annual Scientific Meeting: Americana Hotel, Bar Harbor, Fla. Program Administrator: Lawrence J. Jordan, D.O., Suite 21, Ponce American Bldg., 4601 Ponce de Leon Blvd., Coral Gables, Fla. 33146.

AMERICAN THERMOGRAPHIC SOCIETY
Secretary-Treasurer, John Wallace, Ph.D., Dept. Radiol., Thomas Jefferson Univ. Hosp., Philadelphia, Pa. 19107. Annual Meeting.

ARIZONA RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary, Dr. Robert J. Johnson, 1603 N. Tucson Blvd., Tucson 85716. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meeting six months later.

ARK-LA-TEX RADIOLOGICAL SOCIETY
Secretary, Dr. Erich K. Lang, Confederate Memorial Medical Center, LSU School of Medicine, Shreveport, La. 71101.

ARKANSAS CHAPTER OF ACR
Secretary-Treasurer, Dr. David H. Newbern, 4301 W. Markham, Little Rock, Ark. 72205. Meets twice annually, the Spring Meeting being in conjunction with and at the place of the State Medical Association.

ASSOCIATION OF UNIVERSITY RADIOLOGISTS
Secretary-Treasurer, Dr. Mark M. Mishkin. The Graduate Hosp., Univ. of Pennsylvania, Philadelphia, Pa. 23rd Annual Meeting: San Diego, Calif., May 4–6, 1975.

ATLANTA RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Marshall J. Cantanzaro, Dept. of Radiol., Northside Hosp., Atlanta, Ga. 30342. Meets on fourth Thursday evenings during the academic year at a

*** Secretaries of societies are requested to send timely information promptly to the Editor.**

time announced in early September of each year, at the Academy of Medicine, Atlanta, Ga., at 8:00 P.M.

BAVARIAN-AMERICAN RADIOLOGIC SOCIETY
Secretary, Maj. Marco J. DiBiase, M.D., Radiology Service, 130th Station Hosp., APO N. Y. 09102. Next meeting Dec. 5–8 in Nürnberg, Germany.

BLOCKLEY RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Joseph H. Rosen, West Park Hospital, 3905 Ford Rd., Philadelphia, Pa. 19131.

BLUEGRASS RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Eugene Slusher, Lexington Clinic, 1221 S. Broadway, Lexington, Ky. 40504. The Society meets once each month during the school year.

BRONX RADIOLOGICAL SOCIETY, NEW YORK STATE, CHAPTER ACR
Secretary-Treasurer, Dr. Leon J. Corbin, 1369 Rosendale Ave., Bronx, N. Y. 10472. Meets 4 times a year.

BROOKLYN RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Joshua A. Becker, Downstate Medical Clin., 450 Clarkson Ave., Brooklyn, N. Y. 11203. Meets first Thursday of each month, October through June.

BUFFALO RADIOLOGICAL SOCIETY
Secretary, Dr. George J. Alker, Jr., E. J. Meyer Mem. Hosp., Buffalo, N. Y. 14215. Meets second Monday evening each month, October to May inclusive, at University Club.

CALIFORNIA RADIATION THERAPY ASSOCIATION
Secretary-Treasurer, Dr. James R. Eltringham, Stanford Medical Center, Stanford, Calif. 94304. Meets semiannually in San Francisco and Los Angeles.

CALIFORNIA RADIOLOGICAL SOCIETY, CALIFORNIA CHAPTER of ACR
Secretary-Treasurer, Dr. John L. Gwinn, 4650 Sunset Blvd., Los Angeles, Calif. 90027.

CATAWBA VALLEY RADIOLOGICAL SOCIETY
Secretary, Dr. Walter Joe Jacumin, P.O. Box 265, Rutherford College, N. C. 28671. Meets the last Thursday of every month, Holiday Inn, Morganton, N. C. at 7:30 P.M.

CENTRAL NEW YORK RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Alfred Brettner, Auburn Mem. Hosp., Auburn, N. Y. 13021. Meets first Monday each month October through May.

CENTRAL OHIO RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Daniel E. Lewis, Grant Hosp., Columbus, Ohio 43215. Meets second Thursday in October, November, January, and March 15, and May 19 at Fort Hayes Hotel, Columbus, Ohio.

CENTRAL TEXAS RADIOLOGY SOCIETY
Secretary-Treasurer, Dr. John M. Stoebner, Scott and White Clinic, Temple, Tex. 76501. Meets the fourth Monday of each month at Ponderosa Hotel, Temple, Tex. at 7:00 P.M.

CHICAGO RADIOLOGICAL SOCIETY, DIVISION OF THE ILLINOIS RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary-Treasurer, Dr. Harold J. Lasky, 55 E. Washington St., Suite 1735, Chicago, Ill. 60602. Meets third Thursday of each month, October to April, except December, at the Bismark Hotel, Chicago, Ill.

CLEVELAND RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Charles M. Greenwald, 7007 Powers Blvd., X-Ray Dept., Parma, Ohio 44129. Meetings at 7:00 P.M. on fourth Monday of October, November, January, February, March and fifth Monday of April.

COLORADO RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary, Dr. Jerome D. Sutherland, 3705 E. Colfax Ave., Denver, Colo. 80206. Meets third Friday of each month at Denver Athletic Club from September through May.

CONNECTICUT VALLEY RADIOLOGIC SOCIETY
Secretary, Dr. Gerald N. LaPierre, 759 Chestnut St., Springfield, Mass. 01107. Meets in April and October.

DALLAS-FORT WORTH RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Richard C. Gasser, 1550 W. Rosedale, Rm. 100, Ft. Worth, Tex. 76104. Meets the 3rd Monday of every month at 6:30 P.M., at the Cibola Inn, Arlington, Tex.

DELAWARE CHAPTER OF ACR
Secretary, Dr. Seymour R. Kaplan, Kent Gen. Hosp., Dover, Del. 19901.

EAST BAY RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Robert L. Stein, 43 Dormidera Ave., Piedmont, Calif. 94611. Meets first Thursday each month, Oct. through May, at University Club, Oakland, Calif.

EAST TENNESSEE RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. George H. Wood, 205 Medical Arts Bldg., Knoxville, Tenn. 37902. Meets in January and September.

FLORIDA RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary. Dr. Paul J. Popovich, 1350 S. Hickory St., Melbourne, Fla. 32901. Meets twice annually, in the spring with the annual State Society Meeting and in the fall.

FLORIDA WEST COAST RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. James P. Ahearn, 501 E. Buffalo Ave., Tampa, Fla. 33603. Meets on 4th Thursday of the months January, March, May, October, and November.

GEORGIA RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary, Dr. E. P. Rasmussen, Piedmont Prof. Bldg., 35 Collier Rd., N.W., Atlanta, Ga. 30309.

GREATER CINCINNATI RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Owen L. Brown, 2421 Auburn Ave., Cincinnati, Ohio 45219.

GREATER KANSAS CITY RADIOLOGICAL SOCIETY
President-Secretary, Dr. Keith W. Gallehugh, Bethany Med. Center, Kansas City, Kans. Meets 5 times a year.

GREATER LOUISVILLE RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. L. D. LeNeave, 315 E. Broadway, Louisville, Ky. 40202. Meets monthly.

GREATER MIAMI RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Robert F. Conti, Holy Cross Hosp., Fort Lauderdale, Fla. 33308. Meets monthly, third Wednesday at 8:00 P.M. at various member hospitals, Miami, Fla.

GREATER ST. LOUIS SOCIETY OF RADIOLOGISTS
Secretary-Treasurer, Dr. Donald Callahan, Northland Med. Bldg., Jennings, Mo. 63136.

HAWAII RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary-Treasurer, Dr. Sidney B. W. Wong, Straub Clinic and Hosp., Honolulu, Hawaii 96813. Meets third Monday of each month at 7:30 P.M.

HEALTH PHYSICS SOCIETY
Secretary, Russell F. Cowing, P.O. Box 156, E. Weymouth, Mass. 02189. Annual Meeting.

HOUSTON RADIOLOGICAL SOCIETY
Secretary, Dr. Neill B. Longley, 6436 Fannin, Suite 601, Houston, Tex. 77025. Meets fourth Monday of each month, except June, July, August and December, at 6:00 P.M., at 103 Jesse H. Jones Library Building, Texas Medical Center, Houston, Tex. 77025.

IDAHO STATE RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary-Treasurer, Dr. John H. Truksa, 1605 Park Ave., Nampa, Id. 83651. Meets in the spring and fall.

ILLINOIS RADIOLOGICAL SOCIETY, INC., CHAPTER OF ACR
Secretary, Dr. Robert D. Dooley, Hinsdale Med. Center, Hinsdale, Ill. 60521. Meets in the spring and fall.

INDIANA ROENTGEN SOCIETY, INC., CHAPTER OF ACR
Secretary, Dr. John A. Knote, 716 Carrolton Blvd., West Lafayette, Ind. 47906.

IOWA RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary-Treasurer, Dr. John Huston, Jr., 1948 First Ave., N.E., Cedar Rapids, Iowa 52402. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn.

KANSAS RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary-Treasurer, Dr. Ralph H. Baehr, 310 Medical Arts Bldg., Topeka, Kan. 66604. Meets in spring with State Medical Society and in winter on call.

KENTUCKY CHAPTER OF ACR
Secretary-Treasurer, Dr. Bernard Sams, St. Joseph Infirmary, 735 Eastern Parkway, Louisvlle, Ky. 40217. Meets in April and September.

KINGS COUNTY RADIOLOGICAL SOCIETY
Secretary, Dr. Sidney Hendler, 1880 Ocean Ave., Brooklyn 30, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

KNOXVILLE RADIOLOGICAL SOCIETY
Secretary, Dr. Clifford L. Walton, Blount Professional Bldg., Knoxville 20, Tenn. Meetings are held the third Monday of every other month at the University of Tennessee Memorial Research Center and Hospital.

LONG ISLAND RADIOLOGICAL SOCIETY
Secretary, Dr. Bruce Saxe, 1200 Stewart Ave., Garden City, N. Y. 11533. Meets monthly.

LOS ANGELES RADIOLOGICAL SOCIETY
Secretary, Dr. Isaac Sanders, 1429 Valley View Rd. 13, Glendale, Calif. 91202. Meets second Wednesday of month in September, November, January, April and June at Los Angeles County Medical Association Building, Los Angeles, Calif. Midwinter Radiological Conference: Century Plaza Hotel, Los Angeles, Calif., Jan. 31–Feb. 2, 1975.

LOUISIANA RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary-Treasurer, Dr. Roger H. Tutton, 1514 Jefferson Hwy., New Orleans, La. 70121.

LOUISIANA-TEXAS GULF COAST RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Arnold G. Manske, P.O. Box 3008, Port Arthur, Tex. 71670.

MAINE RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary-Treasurer, Dr. Richard W. Taylor, Radiology Department, St. Mary's General Hospital, Lewiston, Maine 04240. Meets in June, September, December and April.

MARYLAND RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary, Dr. David S. O'Brien, Anne Arundel Hosp., Annapolis, Md. 21401.

MASSACHUSETTS RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary, Dr. Joseph T. Ferrucci, Jr., Massachusetts Gen. Hosp., Boston, Mass. 02114.

MEMPHIS ROENTGEN SOCIETY
Secretary-Treasurer, Dr. Thomas P. Coburn, The University of Tennessee College of Medicine, Department of Radiology, Walter C. Chandler Bldg., 865 Jefferson Ave., Memphis, Tenn. 38163. Meets first Monday Oct. through May at the University Club.

MIAMI VALLEY RADIOLOGICAL SOCIETY
Secretary, Dr. Bert Must, I.B.M. Bldg., Dayton, Ohio. Meets third Thursday of fall, winter and spring months at 7:30 P.M. at Miami Valley Hospital, Dayton, Ohio.

MICHIGAN RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary-Treasurer, Dr. Francis P. Shea, Harper Hospital, 3825 Brush St., Detroit, Mich. 48201. Meets monthly, first Thursday, October through May, at David Whitney House, 1010 Antietam, at 6:30 P.M.

MICHIGAN SOCIETY OF THERAPEUTIC RADIOLOGISTS
Secretary-Treasurer, Dr. Delmar Mahrt, William Beaumont Hosp., Detroit, Mich. 48072. Meets bi-monthly during the academic year.

MID-HUDSON RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. William D. Stiehm, 37 Flower Hill Rd., Poughkeepsie, N. Y. 12603. Meets 7:00 P.M., first Wednesday of each month, September to May.

MILWAUKEE ROENTGEN RAY SOCIETY
Secretary-Treasurer, Dr. Thomas C. Lipscomb, 1004 North Tenth St., Milwaukee, Wis. 53233. Meets monthly on fourth Monday, October through May, at University Club.

MINNESOTA RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary-Treasurer, Dr. Harlan W. Hawkinson, 6 Buffalo Rd., St. Paul, Minn. 55110. Meets twice annually, fall and winter.

MISSISSIPPI STATE RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary-Treasurer, Dr. Edward L. Gieger, 969 Lakeland Dr., Jackson, Miss. 39216. Meets third Thursday, excluding summer months, at the Primos Northgate Rest., Jackson at 6:30 P.M.

MISSOURI RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary-Treasurer, Dr. Ronald G. Evens, Mallinckrodt Institute of Radiology, 510 S. Kingshighway, St. Louis, Mo. 63110.

MONTANA RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary, Dr. C. H. Agnew, Room 102, Doctors Bldg., Billings, Mont. 59101.

NEBRASKA CHAPTER OF ACR
Secretary-Treasurer, Dr. Robert Bodmer, Suite 622 Doctors Bdg., Omaha, Neb. 68131. Meets the third Wednesday of the month, Oct. through March, at the Clarkson Hosp., Omaha, Neb. and the fourth Friday of April at the Lincoln Country Club, Lincoln, Neb.

NEVADA RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary, Dr. Charles F. Veverka, Carson Tahoe Hosp., Carson City, Nev. 89701.

N.E. SOCIETY FOR RADIATION ONCOLOGY
Secretary, Dr. C. C. Wang, Mass. Gen. Hosp., Boston, Mass. 02114.

NEW ENGLAND ROENTGEN RAY SOCIETY
Secretary, Dr. Melvin E. Clouse, 185 Pilgrim Rd., Boston, Mass. 02115. Meets the third Friday of each month, October through April, excluding December, at The Longwood Towers, 20 Chapel Street, Brookline, Mass. at 3:00 P.M. Annual Meeting: May 16, 1975.

NEW HAMPSHIRE ROENTGEN RAY SOCIETY, CHAPTER OF ACR
Secretary-Treasurer, Dr. Edward P. Kane, Claremont Gen. Hosp., Claremont, N. H. 03743. Meets four to six times yearly.

NEW MEXICO SOCIETY OF RADIOLOGISTS, CHAPTER OF ACR
Secretary, Dr. Carole R Simmons, Dept. of Radiol., Presbyterian Hospital Center, Albuquerque, N. M. 87106. Four meetings annually, three held in Albuquerque, N. M., and one held at time and place of New Mexico State Medical Society annual meeting.

NEW ORLEANS RADIOLOGICAL SOCIETY, INC.
Secretary-Treasurer, Dr. Jimmy L. Mains, P.O. Box 446, Gretna, La. 70053. Meets bimonthly at local restaurants selected by the President. Spring Conference.

NEW YORK ROENTGEN SOCIETY
Secretary-Treasurer, Dr. Thomas C. Beneventano, 110 East 210th St., Bronx, N. Y. 10467. Meets monthly on the 3rd Monday at the New York Academy of Medicine at 4:30 P.M. Annual Spring Conference, Waldorf-Astoria Hotel, New York, N. Y., April 24–26, 1975. Further information may be obtained from Dr. Albert A. Dunn, Roosevelt Hosp., New York, N. Y. 10019.

NEW YORK STATE CHAPTER OF ACR
Secretary-Treasurer, Dr. Albert F. Keegan, 6 Secor Dr., Port Wash., N. Y. 11050.

NORTH AMERICAN SOCIETY OF CARDIAC RADIOLOGY
Secretary-Treasurer, Dr. Erik Carlson, Univ. Calif., San Francisco, Calif. 94143.

NORTH CAROLINA CHAPTER OF ACR
Secretary-Treasurer, Dr. Ernest B. Spangler, Wesley Long Hosp., Greensboro, N. C. 27402. Meets twice a year. The Spring Meeting is held at the time of the meeting of the North Carolina Medical Society. The Fall Meeting is held in November at the Mid Pines Club, Southern Pines, N. C.

NORTH DAKOTA RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary, Dr. Pablo Ramos, Box 1618, Bismarck, N. D. 58501. Meets at time of State Medical Association meeting. Other meetings arranged on call of the President.

NORTH FLORIDA RADIOLOGICAL SOCIETY
Secretary, Dr. David F. Bew, University Hospital of

Jacksonville, 655 W. Eighth Street, P.O. Box 2751, Jacksonville, Fla. 32203. Meets quarterly in March, June, September and December.

Northeastern Oklahoma Radiological Society
Secretary-Treasurer, Dr. Theodore J. Brickner, Jr., 5919 S. Gary Place, Tulsa, Okla. 74110.

Northeastern New York Radiological Society
Secretary, Dr. Donald R. Morton, Dept. of Radiology, St. Clare's Hosp., Schenectady, N. Y. 12304. Meets in Albany area on third Wednesday of October, November, March, April, and May.

Northern California Radiation Therapy Association
Secretary-Treasurer, Dr. James R. Eltringham, Stanford Medical Center, Stanford, Calif. 94304. Meets quarterly.

Northern California Radiological Society
Secretary, Dr. Mark D. Reiss, 5301 F Street, Sacramento, Calif. 95819. Meets on the fourth Monday of Sept., Nov., Jan., March and May at the Mansion Inn, Sacramento, Calif.

Northwestern New York Radiological Society
Secretary, Dr. Barbara E. Chick, Glens Falls Hospital, Glens Falls, N. Y. 12801.

Northwestern Ohio Radiological Society
Secretary, Dr. Doug Ki Cho, 2730 Navarre Ave., Oregon (Toledo), Ohio 43616. Meets 3rd Wednesday from September to May.

Ohio State Radiological Society, Chapter of ACR
Secretary, Dr. Tearle L. Meyer, 175 S. Merkle Rd., Columbus, Ohio 43215.

Oklahoma State Radiological Society, Chapter of ACR
Secretary, Dr. George H. Ladd, 4616 Denison, Muskogee, Okla. 74401. Meets in January, May and October.

Orange County Radiological Society
Secretary, Dr. Marvin A. Rawitch, 600 E. Washington, Santa Ana, Calif. 92701. Meets on fourth Tuesday of the month, excluding June, July, August, and December, at Orange County Medical Association Bldg., Orange, Calif.

Oregon State Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Robert E. Craven, P.O. Box 12542, Portland, Ore. 97212. Meets on second Wednesday of month, October through April, at the University Club, Portland, Ore.

Orleans Parish Radiological Society
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans, La. 70113. Meets second Tuesday of each month.

Pacific Northwest Radiological Society
Secretary-Treasurer, Dr. Betty J. Wood, Dept. of Radiol., Vancouver General Hosp., Vancouver 9, B. C., Canada. Annual Meeting.

Pennsylvania Radiological Society, Chapter of ACR
Secretary, Dr. Robert B. Funch, Germantown Hosp., Philadelphia, Pa. 19144.

Philadelphia Roentgen Ray Society
Secretary, Dr. Marvin E. Haskin, 230 N. Broad St., Philadelphia, Pa. 19102. Meets first Thursday of each month at 5 P.M., from October to May in Thompson Hall, College of Physicians.

Pittsburgh Roentgen Society
Secretary, Dr. Klaus M. Bron, Presbyterian-Univ. Hosp., Pittsburgh 15213. Meets second Wednesday of month, September through May, at the Pittsburgh Athletic Association.

Radiation Research Society
Executive Secretary, Richard J. Burk, Jr., 4211 39th St., N.W., Washington, D. C. 20016. Annual Meeting.

Radiological Society of Connecticut, Inc., Chapter of ACR
Secretary-Treasurer, Dr. Mehdi S. Eslami, 1389 W. Main St., Waterbury, Conn. 06708.

Radiological Society of Greater Cincinnati
Secretary-Treasurer, Dr. Alvin Nathan, c/o Academy of Medicine, 320 Broadway, Cincinnati, Ohio 45202. Meets first Monday of each month at Cincinnati Academy of Medicine.

Radiological Society of New Jersey, Chapter of ACR
Secretary, Dr. Sidney Ketyer, St. Elizabeth Hosp., 225 Williamson St., Elizabeth, N. J. 07207. Meets in Atlantic City at time of State Medical Society meeting and in October or November in Newark, N. J.

Radiological Society of Rhode Island, Chapter of ACR
Secretary-Treasurer, Dr. Daniel J. Alves, Rhode Island Hosp., Providence, R. I. 02902.

Radiological Society of Southern California
Secretary-Treasurer, Dr. Marshall Rowen, Dept. Radiol., St. Joseph Hosp., 1100 Stewart Dr., Orange, Calif. 92668. Meets three times a year, usually October, February and May.

Radiological Society of the State of New York
Secretary-Treasurer, Dr. John W. Colgan, 273 Hollywood Ave., Rochester, N. Y. 14618.

Redwood Empire Radiological Society
Secretary, Dr. Charles E. Carter, 121 Sotoyome St., Santa Rosa, Calif. 95405. Meets second Monday every other month.

Richmond County Radiological Society
Secretary, Dr. Donald P. King, 218 Gun Club Rd., Richmond, Va. 23221. Meets first Thursday of each month at various hospitals.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary-Treasurer, Dr. Robert J. Bruneau, 1441 East Ave., Rochester, N. Y. 14610. Quarterly meetings on the call of the President, at the Rochester Academy of Medicine.

Rocky Mountain Radiological Society
Secretary-Treasurer, Dr. Lorenz R. Wurtzebach, 4200 E. Ninth Ave., Denver, Colo. 80220. Annual meeting: Brown Palace Hotel, Denver, Colo., Aug. 1975.

San Antonio-Civilian Military Radiological Society
Secretary, Dr. James R. Stewart, Oak Hills Medical Ctr., San Antonio, Tex. 78209. Meets third Wednesday of each month at Fort Sam Houston Officers Club at 6:30 P.M.

San Diego Radiological Society
President, Dr. Stanley G. Seat, 476 Prospect St., LaJolla, Calif. 92037. Meets the first Wednesday of each month at the University Club.

San Francisco Radiological Society
Secretary-Treasurer, Dr. Charles A. Gooding, Univ. of Calif. Med. Ctr., San Francisco, Calif. 94122.

Section on Radiology, California Medical Association
Secretary, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

Section on Radiology, Medical Society of the District of Columbia
Secretary-Treasurer, Dr. Albert M. Zelna, 21 Masters St., Potomac, Md. 20854. Meets at Medical Society Library, third Wednesday of January, March, May and October at 8:00 P.M.

Section of Radiology, National Medical Association
Secretary, Dr. Ruby Brooks, Dept. Radiol., Veterans Adm. Hosp., P.O. Box 511, Tuskogee, Ala. 36083. Annual Meeting.

Section on Radiology, Southern Medical Association
Secretary, Dr. Mario A. Calonje, 1514 Jefferson Highway, New Orleans, La. 70121. Annual Meeting.

Section on Radiology, Texas Medical Association
Secretary, Dr. George F. Crawford, St. Elizabeth Hospital, Beaumont, Tex. Meets annually with the Texas Medical Association.

Shreveport Radiological Club
Secretary, Dr. W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday at 7:30 P.M., September to May inclusive.

Society for Pediatric Radiology
Secretary-Treasurer, Dr. John P. Dorst, 601 N. Broadway, Baltimore, Md. 21205. Annual meeting: Marriott Hotel, Atlanta, Ga., Sept. 28–29, 1975.

Society of Gastrointestinal Radiologists
Secretary-Treasurer, Dr. John R. Amberg, Vanderbilt University Hospital, Nashville, Tenn. 37232.

Society of Nuclear Medicine
Secretary, Dr. E. James Potchen, Edward Mallinckrodt Institute of Radiology, 660 S. Euclid Ave., St. Louis, Mo. 63110. *Administrative Officer*, Mrs. Margaret Glos, 211 E. 43rd St., New York, N. Y. 10017. Annual Meeting.

South Bay Radiological Society
Secretary, Dr. John H. Callaghan, Redwood Med. Clinic, 2900 Whipple Ave., Redwood City, Calif. 94062. Meets the 2nd Monday of each month at the Santa Clara County Medical Association Bldg., 700 Empey Way, San Jose, Calif.

South Carolina Radiological Society, Chapter of ACR
Secretary, Dr. George W. Brunson, 1406 Gregg St., Columbia, S. C. Annual meeting (primarily business) in conjunction with the South Carolina Medical Association meeting in May. Annual fall scientific meeting at time and place designated by the president.

South Coast Radiological Society Chapter of ACR
Secretary-Treasurer, Dr. Richard T. Love, Santa Barbara Med. Clin., 215 Pesetas Lane, Santa Barbara, Calif. 93110. Meets fourth Tuesday of alternate months, Sept., Nov., Jan., March and May.

South Dakota Radiological Society, Chapter of ACR
Secretary, Dr. M. F. Petereit, 2416 S. Phillips, Sioux Falls, S. D. 57105. Meets in spring with State Medical Society and in fall.

Southern California Radiation Therapy Society
Secretary-Treasurer, Dr. Duane J. Gillum, 250 W. Pueblo St., Santa Barbara, Calif. 93105. Meets quarterly.

Southern Radiological Conference
Secretary-Treasurer, Dr. Marshall Eskridge, Mobile Infirmary, P.O. Box 7544, Mobile, Ala. 36607. Annual Meeting: Grand Hotel, Point Clear, Ala., January 31–February 2, 1975.

Southwestern Radiological Society
Secretary, John M. McGuire, 904 Chelsea, El Paso, Tex. Meets last Monday of each month at 6:30 P.M. in the Paso del Norte Hotel.

Tennessee Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Charles W. Kimsey, 111 Whitehall Bldg., 960 E. Third St., Chattanooga, Tenn. 37403. Meets annually at the time and place of the Tennessee State Medical Association meeting.

Texas State Radiological Society, Chapter of ACR
Secretary, Dr. Francis E. O'Neill, 1128 Nix Prof. Bldg., San Antonio, Tex. 78205.

The Fleischner Society
Secretary, Dr. E. Robert Heitzman, State University of New York Upstate Medical Center, Syracuse, N. Y. 13210. Annual Meeting: St. Francis Hotel, San Francisco, Calif., May 28–31, 1975.

Tri-State Radiological Society
Secretary, Dr. John H. Marchand, Jr., Methodist Hospital, Henderson, Ky. Meets third Wednesday of Oct., Jan., March and May, 8:00 P.M., Elks Club in Evansville, Ind.

Upper Peninsula Radiological Society
Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

Utah State Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Thomas K. Orton, St. Mark's Hosp., Salt Lake City, Utah 84117. Meets fourth Wednesday in January, March, May, September and November at Holy Cross Hospital.

Vermont Radiological Society, Chapter of ACR
Secretary, Dr. J. Lorimer Holm, R.R. #3, Barre, Vt. 05641.

Virginia Chapter of ACR
Secretary-Treasurer, Dr. Charles P. Winkler, 3500 Kensington Ave., Suite 2-A, Richmond, Va. 23221.

Washington, D. C., Chapter of ACR
Secretary-Treasurer, Dr. Robert M. Allen, 9312 Convento Terr., Fairfax, Va. 22030.

Washington State Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Donald J. Hesch, 3216 N. E. 45th Place, Seattle, Wash. 98105.

West Virginia Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Andrew W. Goodwin, II, 200 Med. Arts Bldg., Charleston, W. Va. 25301. Meets concurrently with annual meeting of West Virginia State Medical Society, other meetings arranged by program committee.

Westchester County Radiological Society
Secretary, Dr. James O. Richardson, Jr., 280 Mamaronek Ave., White Plains, N. Y. 10605. Meets on second Tuesday of October, December, February and May.

Wisconsin Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. June Unger, Wood VA Hosp., Wood, Wis. 53193. Meets twice a year, May and September.

Wisconsin Society of Therapeutic Radiologists
Secretary, Dr. Alvin Greenberg, Radiother. Ctr., Univ. Hospitals, Madison, Wisc. 53706. Meets quarterly.

Wyoming Radiological Society, Chapter of ACR
Secretary, Dr. Ross J. Collie, Box 96, Lander, Wyo. 82520. Meets in fall with State Medical Society and in spring on call of President.

Mexico, Puerto Rico and Central America

Asociación Costarricense de Radiología
Secretary, Dr. Rafael Umaña-Umaña, Apartado 8-5340, San José, Costa Rica.

Asociacón de Radiólogos de Centro America y Panamá. Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá
Secretary-General, Dr. Francisco Miranbell Solis, Apartado 3352, San José, Costa Rica, Central America. Meets annually in a rotating manner in the six countries.

Asociación Puertorriqueña de Radiología
Secretary, Dr. R. B. Díaz Bonnet, Suite 504, Professional Bldg., Santurce, Puerto Rico.

Sociedad de Radiología de Salvador
Secretary, Dr. Carlos Meijia, 5a Av. Nte. No. 434, San Salvador, Rep. El Salvador.

Sociedad de Radiología de Guatemala
Secretary, Dr. Carlos E. Escobar, 9ª. Calle A 0–05, Zona 1, Guatemala

Sociedad Mexicana de Radiología, A.C.
Coahuila No. 35, México 7, D.F., México.
Secretary-General, Dr. Jorge Cano Coquí. Meets first Monday of each month.

Sociedad Radiológica Panameña
Secretary, Dr. L. Arrieta Sánchez, Apartado No. 6323, Panamá, R. de P. Meets monthly in a department of radiology of a local hospital chosen at preceding meeting.

Sociedad Radiológica de Puerto Rico
Secretary, Dr. Heriberto Pagán Sáez, Box 9387, Santurce, Puerto Rico. Meets second Thursday of each month at 8:00 P.M. at the Puerto Rico Medical Association Bldg. in San Juan.

British Commonwealth of Nations

Association of Radiologists of the Province of Quebec
121 Boul. Taschereau, Greenfield Park, P. Q., Canada. Meets four times a year.

British Institute of Radiology
Honorary Secretaries, D. H. Traspnell, M. Cohen, 32 Welbeck St., London, W1M/7PG, England.

Canadian Association of Physicists, Division of Medical and Biological Physics
Honorary Secretary-Treasurer, Dr. R. G. Baker, Ontario Cancer Foundation, Ottawa Civic Clinic, 1053 Carling Ave., Ottawa 3, Ont., Canada.

Canadian Association of Radiologists
Honorary Secretary, Dr. Ross O. Hill, Suite 806, 1440 St.

Catherine St. West, Montreal 107, Que., Canada. Annual Meeting: Toronto, Ont., May 11–16, 1975.

Edmonton and District Radiological Society
Secretary, Dr. L. A. Koller, Suite 360, Professional Bldg., 10830 Jasper Ave., Edmonton 15, Alberta, Canada. Meets third Thursday of each month October to May, except December, at various Edmonton Hospitals.

Faculty of Radiologists
Honorary Secretary, J. W. Laws, Lincoln's Inn Fields, London WC2A 3PN, England.

Montreal Radiological Study Club
Secretary, Dr. W. Paul Butt, Montreal General Hospital, Montreal, Que., Canada. Meets first Tuesday evening, October to April.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets third Friday each month at 8:15 P.M. at the Royal Society of Medicine, 1 Wimpole St., London, W. 1 M8AE, 1 England.

Société Canadienne-Française de Radiologie
Secretary-General, Dr. Hubert Sasseville, Verdun Hospital, Montréal, P. Q., Canada. Meets every third Tuesday from October to April.

The Hospital Physicists' Association
Honorary Secretary, J. B. Massey, B.Sc., Christie Hosp. and Holt Radium Institute, Physics Department, Withington, Manchester M20 9BX, England.

Toronto Radiological Society
Secretary, Dr. George Wortzman, Toronto General Hosp., Toronto 12, Ont., Canada. Meets second Monday of each month, September through May.

The Royal Australasian College of Radiologists
Honorary Secretary, Dr. T. P. Loneragan, 45 Macquarie St., Sydney, N.S.W. 2000, Australia.

South America

Colégio Brasileiro de Radiologia
Secretary-General, Dr. Lauro de Abreu Coutinho, Caixa Postal 5984, São Paulo, Brazil.

Federación Argentina de Sociedades de Radiología
Branches of the Federation are: Sociedad de Radiólogos de la Provincia de Córdoba; Sociedad Argentina de Radiología; Asociación Argentina de Radiología; Sociedad de Radiología, Radioterapéutica y Medicina Nuclear de Rosario; Sociedad de Radiología y Medicina Nuclear del Centro y Sudeste de la Provincia de Buenos Aires (Mar del Plata); Sociedad Salteña de Radiología y Medicina Nuclear; Sociedad de Radiología de Tucumán; Sociedad de Radiologia del Nordeste Argentino; Sociedad de Radiología de La Plata; and Sociedad de Radiología de San Juan.
Secretary-General-Treasurer, Dr. Roberto Habichayn, Av. Colón 637, Córdoba, Argentina.
Congress will be organized by Sociedad de Radiología, Radioterapéutica y Medicina Nuclear de Rosario in 1975.

Sociedad Argentina de Radiología
Secretary-General, Dr. Tomás J. Gutiérrez F, Santa Fé 1171, Buenos Aires, Argentina. Meets first Wednesday evening, April through December.

Sociedad Boliviana de Radiología
Secretary, Dr. Javier Prada Méndez, Casilla 1182, La Paz, Bolivia. Meets monthly. General assembly once every two years.

Sociedade Brasileira de Radiologia
Secretary, Dr. Armando Rocha Amoédo, Caixa Postal 1532, Rio de Janeiro, Brazil. General Assembly meets every two years in December.

Sociedade Brasileira de Radioterapia
Luiz Antonio, 644, São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Chilena de Radiología
Secretary, Dr. Manuel Neira, Casilla 13426, Santiago, Chile. Meets first Friday of each month at Av. Santa María 1810 at 7:00 P.M.

Sociedad Colombiana de Radiología
Secretary-General, Dr. Gustavo Sánchez Sánchez, Bogotá, Colombia. Meets last Thursday of each month.

Sociedad Ecuatoriana de Radiología
Secretary, Dr. Luis Blum, Casilla 3712, Guayaquil, Ecuador.

Sociedad Paraguaya de Radiología
Secretary, Dr. Hugo Volpe Rios, 15 de Agosto 322, Asunción, Paraguay.

Sociedad Peruana de Radiología
Secretary-General, Dra. Ladis Delpino, Av. General Santa Cruz No. 315, Miraflores, Lima, Perú, Casilla Correo, 2306, Lima, Perú. Meets monthly except during January, February, and March.

Sociedad de Radiología del Atlantico
Secretary, Dr. Raul Fernandez, Calle 40 #41-110, Baranquilla, Colombia. Society meets monthly at the Instituto de Radiología.

Sociedad de Radiología del Nordeste Argentino
Secretary-General, Dr. Francisco J. Velar, Catamarca 561, Corrientes, Argentina.

Sociedad de Radiología de La Plata
Secretary, Dr. Hiram D. Haurigot, Calle 50 No. 374, La Plata, Argentina.

Sociedad de Radiología, Cancerología y Física Médica del Uruguay
Secretary-General, Dr. Manuel Gonzáles Maseda, Av. Agraciada 1464, piso 13, Montevideo, Uruguay.

Sociedade de Radiología de Pernambuco
Secretary, Dr. Manoel Medeiros Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife, Caixa Postal 505, Pernambuco, Brazil.

Sociedad de Roentgenología y Medicina Nuclear de la Provincia de Córdoba
Secretary-General, Dr. Lucas C. Di Rienzo, Ave. Grl. Paz. 151, Córdoba, Argentina.

Sociedad de Radiología, Radioterapéutica y Medicina Nuclear de Rosario
Secretary-General, Dr. Federico Frágola, Santa Fe 1798, Rosario, Argentina.

Sociedad Salteña de Radiología y Medicina Nuclear
Treasurer, Dr. Julio Luis Baldi, Av. Sarmiento 536, Salta, Argentina.

Sociedad Venezolana de Radiología y Medicina Nuclear
Secretary-General, Dr. Salvador Itriago Borgas, Apartado Postal 9213, Candelaria, Caracas, Venezuela. Meets monthly, third Friday at Colegio Médico del Distrito Federal, Caracas.

Continental Europe

Österreichische Röntgen-Gesellschaft
Secretary, Dr. Ernst Kotcher, Wiener Allgemeine Poliklinik Mariannengasse 10, A-1090 Wien, Austria. Meets second Tuesday of each month in Allgemeine Poliklinik.

Société Royale Belge de Radiologie
General Secretary, Dr. Joseph Baeyens, Alost, Belgium. Meets in February, March, May, June, September, October, November and December.

Société Européenne de Radiologie Pédiatrique
Secretary, Dr. J. Corbaton, Clinica Infantil "La Paz," Av. Generalissimo, 117 Madrid 34, Spain. Annual Meeting: Madrid, Apr. 24–26, 1975.
Permanent Secretary, Clément Fauré, Hôpital des Enfants Malades, 149, rue de Sèvres, 75 730, Paris Cadet 15, France.

Société Française de Radiologie Médicale, Médecine Nucléaire et Électrologie, and its branches: Société du Sud-Ouest, du Littoral méditerranéen, du Centre et Lyonnais, du Nord, de l'Ouest, de l'Est, du Massif Central, d'Outre-Mer et d'Étranger. Parent Society meets third Monday of each month, except during July, August and September, rue de Seine 12, Paris, France.
Secretary-General, Dr. Ch. Proux, 9 rue Daru, Paris 75008, France.

Société Française de Neuroradiologie
Secretary-General, Professeur agr. R. Djindjian 16, rue de l'Université 75, Paris 7e, France. Annual meeting.

Československá Radiologická Společnost
Secretary, Associate Professor Jaromír Kolář, M.D., Sc.D., Radiological Clinic, Praha 2, U nemocnice 2, Czechoslovakia. Meets monthly except during July, August and September. Annual general meeting.

Deutsche Röntgengesellschaft
President, Professor Dr. med. Walter Frommhold, Director of Medizinisches Strahleninstitut der Universität Tübingen, Röntgenweg 11, 7400 Tübingen, Germany.

Faculty of Radiologists of the Royal College of Surgeons in Ireland
Honor. Secretary, Max. J. Ryan, St. Stephen's Green, Dublin 2. Annual Meeting, Oct. 25 and 26, 1974.

Società Italiana di Radiologia Medica e Medicina Nucleare
Administrative Secretary, Prof. E. Conte, Ospedale Mauriziano, 10128 Torino, Italy. Meets annually.

Societas Radiologica Danica
Secretary, Dr. Bent Langenfeldt, Tretommervej 20a, DK. 8240 Risskov, Denmark.

Nederlandse Vereniging voor Radiologie
Secretary, Dr. J. D. Mulder, Dept. of Rad., Akademisch Ziekenhuis, Leiden, Netherlands.

Scandinavian Radiological Society
Secretary-General, Professor C. F. Unnérus, M.D., Hagalung-Tapiola, Havsvindsvägn 5 C., Finland. Annual Meeting.

Sociedad Española de Radiología y Electrología Médicas y de Medicina Nuclear
Secretary, Dr. José Bonmatí, Villanueva, 11, Madrid 1, España. Meets every second Friday of each month, Oct. to June, inclusive, in Madrid.

Sociedade Portuguesa de Radiologia e Medicina Nuclear
Secretary-General, Dr. Luís Aires de Sousa, Av. Elias Garcia, 123- 1, Esg.-Lisboa 1-Portugal.

Schweizerische Vereinigung für Radiologie, Nuklearmedizin und Strahlenbiologie (Association Suisse de Radiologie, Médecine Nucléaire et de Radiobiologie)
Secretary, Dr. med. Gustav Schoch, Bethesdaspital, Gellerstrasse 144, 4000 Basel, Switzerland.

Asia

Indian Radiological Association
Honor. Gen. Secretary, Dr. S. P. Aggarwal, 10-B Kasturba Ghandi Marg, New Delhi 110001. 28th Indian Congress of Radiology will be held in Hyderabad in 1975.

Indonesian Radiological Society
Secretary, Dr. Gani Iljas Sasmitaatmadja, Radiology Dep., Faculty of Medicine, University of Indonesia, Salemba 6, Jakarta, Indonesia.

Iranian Radiological Society
Secretary, Dr. Majid Rooholamini, P.O. Box No. 14-1151, Teheran, Iran. The Society meets on the second Saturday of each month. 5th Iranian Congress of Radiology, Apr. 12–17, 1975. Deadline for acceptance of papers, Jan. 20, 1975.

Israel Radiological Society
Secretary, Dr. M. A. Lerner, Hesharon Hosp., Petah-Tigva, Israel.

Philippine College of Radiology
Secretary-Treasurer, Dr. Eduardo V. Nievera, Box 1284 Commercial Center, Makati, Rizal D-708, Philippines. Meets every second Thursday of the month.

Radiological Society of Thailand
Secretary, Prof. Rojana Suvansuthi, M.D., Ph.D., Depart. of Rad., Sirizaj Hospital, Faculty of Medicine, Mahidol University, Bangkok 7, Thailand.

Africa

Association of Radiologists of West Africa
Honorary Secretary, C. A. Beetlestone, M.B., B.S., D.M.R.D., Dept. Radiol., University College Hosp., Ibadan, Nigeria. Thirteenth Annual Conference, in Ibadan, Feb. 8–10, 1975. Conference Secretary: Dr. A. O. Sobo, The J. F. Kennedy Medical, P. O. Box 1973, Monrovia, Liberia.

Radiological Society of South Africa
Secretary, Dr. B. Rosenberg, P.O. Box 3200, Johannesburg, South Africa.

South African International Radiological Congress
Director, Dr. Paul Sneider, P.O. Box 4878, Johannesburg, South Africa.

Vol. 123, No. 1

ABSTRACTS OF RADIOLOGIC LITERATURE

E. FREDERICK LANG, M.D., Editor

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ROENTGEN DIAGNOSIS

Head

Batnitzky, Solomon, Sarwar, Mohammad, Leeds, Norman E., Schechter, Mannie M., and Azar-Kia, Behrooz. Colloid cysts of the third ventricle. *Radiology*, Aug., 1974, *112*, 327–341. (Address: Solomon Batnitzky, M.D., Department of Radiology, Albert Einstein College of Medicine, Bronx, N. Y. 10461.)

Colloid cysts are considered by Bull and Sutton as *the* tumor of the third ventricle. In the past, colloid cysts of the third ventricle were not diagnosed during life. This rather extensive and inclusive article deals with the pathogenesis, pathology, clinical presentation, radiology, and differential diagnosis of colloid cysts of the third ventricle.

The colloid cyst is shrouded with controversy regarding its site of origin. The most accepted view with regard to the origin of the colloid cyst is that of Kappers, and also Coxe and Luse. This view indicates that colloid cysts arise from diencephalic ependymal pouches. The cysts arise in the anterior superior aspect of the third ventricle immediately posterior and adjacent to the foramina of Monro. The cyst is sharply circumscribed and varies in size from 3 mm. to 40 mm. The largest cyst reported in the literature was 9 cm.

The clinical material deals with 25 cases of histologically proved colloid cysts and 2 additional cases without colloid cysts which show pitfalls in the radiologic diagnosis of colloid cysts. The clinical features cover a rather wide spectrum of symptoms. Lesions elsewhere in the brain may produce similar signs and symptoms. Both sexes are affected equally. The cyst produces symptoms by obstructing the flow of CSF with resultant intermittent and paroxysmal attacks of headache, vomiting, diplopia and blurred vision. This particular clinical picture is most suggestive of a colloid cyst. Of all intracranial tumors, a colloid cyst is one of the most favorable for removal surgically. The diagnosis rests upon radiologic techniques and ventriculography is the most useful.

Radiologically, plain film roentgenograms of the skull are nonspecific and may show only those findings associated with increased intracranial pressure. Colloid cysts do not calcify. Calcifications in the region of the foramen of Monro should lead one away from the diagnosis of the colloid cysts. Angiography and intracranial air studies are more definitive in the diagnostic work-up. Angiography will reveal hydrocephalus, using the classic findings of increased sweep of the pericallosal artery and outward bowing of the thalamostriate vein in the frontal venous phase. Ventriculography is the most definitive examination and is the procedure of choice because of the fact that the majority of cases of colloid cyst have elevated intracranial pressure. The brow-up position is the best for the demonstration of the midline lesion. A variant of the brow-up (hanging head view) is also often used. The cyst presents as a soft tissue density mass projecting into the floor of the lateral ventricles. The circumference of the cyst can be almost totally outlined. It is located posterior to the foramina of Monro and anterior to the massa intermedia. The foramina may be narrowed or displaced slightly anteriorly. The anteroposterior and lateral projections with the brow-up technique are most satisfactory. Cavum septum pellucidum may also occur with the colloid cyst.

Differential diagnosis should include aneurysm arising from the tip of the basilar artery. A rather large massa intermedia may also simulate a colloid cyst. Third ventricular meningiomas, ependymomas, choroid plexus papillomas, teratoid tumors, suprasellar masses, tuberus sclerosis nodules, and parasitic involvement are all differential possibilities. A thorough discussion of the differential possibilities is presented in the article.

An extensive bibliography is given.—*J. P. Eberts, M.D.*

Marc, Joseph Alan, and Schechter, Mannie M. Cortical venous rerouting in parasagittal meningiomas. *Radiology*, July, 1974, *112*, 85–91. (Address: Joseph Alan Marc, M.D., Department of Radiology, Division of Neuroradiology, Emory University, Grady Memorial Hospital, Atlanta, Ga. 30303.)

Angiograms of 22 cases of proven parasagittal meningiomas were studied in retrospect. All had surgical confirmation of occlusion or compression of the superior sagittal sinus by the tumor. Four case histories are presented. Fourteen of the 22 patients exhibited angiographic findings of occlusion or severe compression of the superior sagittal sinus. Since the surgical approach of parasagittal tumors is affected by the patency of the superior sagittal sinus, it is important to attempt to determine the status of the superior sagittal sinus.

The lateral venous phase roentgenograms are the most important to predict occlusion or severe compression. Findings must include: (1) nonvisualization of a segment of the superior sagittal sinus; (2) failure of cortical veins to reach the superior sagittal sinus; (3) delayed emptying of veins in the area of obstruction; (4) reversal of normal venous flow with collateral venous channels connecting the superior sagittal sinus anterior to the obstruction to one of the following: (a) the superior sagittal sinus posterior to the obstruction, (b) lateral sinus, (c) middle cerebral vein, and (d) deep venous system.

Certain conditions mimic partial obstruction of the superior sagittal sinus. These include absence of the anterior part of the superior sagittal sinus as a nor-

mal variant. This is replaced by a large cortical vein or an intradural venous channel. Nonvisualization of a portion of the superior sagittal sinus without the other signs may be due to a large amount of unopacified blood from the opposite hemisphere. This may be resolved by cross-compression.—*A. K. Teaford, M.D.*

Neck and Chest

Trecate, Franca Ferrari, and Scaravelli, Corrado. Contributo alla possibilità di formulare diagnosi radiologica di micetoma polmonare. (Contribution to the roentgen diagnosis of pulmonary mycetoma.) *Radiol. med.*, Feb., 1974, *60*, 118–123. (Address: Dr. Franca Ferrari Trecate, Dalla Divisione Radiologica, Ospedale G. Salvini, I-20020 Garbagnate Milanese, Milan, Italy.)

The roentgen appearance of the intracavitary inclusion of a pulmonary mycetoma is given by a moderately dense parenchymal roundish or oval mass, rather homogeneous with well defined contours and partially surrounded by a semilunar band of radiolucency. At times, however, one notes a true cavity with thick walls and which contains the fungus ball.

If the differential diagnosis is between a pulmonary mycetoma and, for example, a lung abscess, a primary or secondary cavitating carcinoma and a tuberculous cavity, the characteristics of the outer and inner walls of the cavity do not always lead to the correct diagnosis. It is the mobility of the intracavitary mass which is of diagnostic importance.

The authors have demonstrated the presence of a fungus ball in 2 cases by examining the patients in the upright and Trendelenburg positions with roentgen tomography and also by observing fluoroscopically the change in position of the intracavitary mass, while the patients were asked to breathe deeply and to cough. The advantages of the tomographic study in the Trendelenburg position are clearly demonstrated by the reproductions which accompany the article.—*A. F. Govoni, M.D.*

Corrigan, T. P., Fossard, D. P., Spindler, J., Armstrong, P., Strachan, C. J. L., Johnston, K. W., and Kakkar, V. V. Phlebography in the management of pulmonary embolism. *Brit. J. Surg.*, June, 1974, *61*, 484–488. (Address: Dr. V. V. Kakkar, Departments of Surgery and Radiology, King's College Hospital Medical School, Denmark Hill, London SE5, England.)

Ascending phlebography, chest roentgenography, and perfusion lung scanning were performed in 102 patients suspected of pulmonary embolism. Of 33 patients with a high probability of pulmonary embolism by perfusion lung scanning, 87 per cent had thrombi in the peripheral veins. In 45 patients with a low probability of pulmonary emboli, 33 per cent had peripheral vein thrombi. Ascending phlebography provided good opacification of the deep veins of the lower extremity and iliac veins were well visualized in 190 of the 194 limbs examined.

Ascending phlebography was useful in patient management, particularly in those with negative lung scans, in whom anticoagulants were required for treatment of thrombi in peripheral veins. It is unfortunate that pulmonary angiography was not done in more patients, particularly in those with high probability lung scans and negative phlebograms. While the authors conclude that most pulmonary emboli arise from thrombi in the leg, it is possible that some of the patients with high probability lung scans had thrombi arising in the pelvis or heart.

The authors further concluded that when pulmonary angiography cannot be performed or when the initial symptoms are of a minor nature, ascending phlebography can be utilized as a diagnostic procedure to document the presence or absence of a potential site for emboli. For those patients with high probability lung scans and normal phlebograms, pulmonary angiography should be performed since these patients can have pulmonary emboli arising from an alternative site.—*Robert I. White, Jr., M.D.*

Marčinski, A., Cieslak, H., and Swiatkowska, I. Mesothelioma of the pleura in children. *Ann. de radiol.*, May–June, 1974, *17*, 327–333. (Address: Dr. A. Marčinski, Zaklad Radiologii Pediatrycznej, Marszalkowska 24, Warszawa, Poland.)

Three childhood cases of the rare mesothelioma of the pleura are reported. The children were 7, 11, and 14 years old, respectively; each presented with dyspnea, had abnormal chest roentgenograms, had diffuse malignant mesothelioma and had no effective therapy.

Mesothelioma usually arises from pleura tissue, but can also originate from serous membranes, *e.g.*, peritoneum or exceptionally pericardium. The tumor in the pleura may be a solitary benign tumor or a diffuse malignant one. In the latter circumstance, chest roentgenograms may demonstrate large quantities of pleural fluid and/or pleural tumor masses associated with destruction of the adjacent rib portions.

Thoracic angiography may prove valuable since that examination may show more precisely the size of the tumor and its relation to adjacent thoracic structures.

Treatment is very difficult and in diffuse malignant forms is usually a failure.—*Lionel W. Young, M.D.*

Stein, Paul D., Lewinson, Henri, and Potts, Kent H. Cardiac size and left ventricular performance: lack of correlation with silhouette measurement. *J.A.M.A.*, Sept., 1974, *229*, 1614–1620. (Address: Paul D. Stein, M.D., Veterans Administration Hospital, 921 NE 13th Street, Oklahoma City, Okla. 73104.)

Chest roentgenograms of 75 patients with ischemic heart disease proved by selective coronary arteriography were correlated with hemodynamic measurements and left ventricular angiography. A variety of measurements of left ventricular size were applied to the chest roentgenograms and then correlated with left ventricular end-diastolic pressure, left ventricular circumferential fiber shortening, and fiber shortening rate. Transfrontal plane transverse diameter, oblique diameter and cardiothoracic ratio were often normal in patients with moderate-to-severe impairment of left ventricular function. If the cardiac silhouette was enlarged, the authors could reliably predict that left ventricular function was impaired.

The authors conclude that in the patient with coronary heart disease, the physician must be aware that the size and symptoms of poor ventricular function may exist in the presence of a normal cardiac silhouette. This concept, of course, is not new, since many previous studies have documented that congestive heart failure in the presence of a normal cardiac silhouette usually implies ischemic heart disease.—*Robert I. White, Jr., M.D.*

Bundi, R. Sushila. Chemodectomas. *Clin. Radiol.*, July, 1974, *25*, 293–302. (Address: Radiotherapy Department, North Ormesby Hospital, Middlesbrough, TS3 6HJ, England.)

Chemodectoma is a rare tumor of chemoreceptor tissue located along blood vessels and nerves. This report reviews 25 cases of chemodectomas of the glomus jugulare (19), carotid body (4), aortic body (1), and the larynx (1).

Tumors of the chemoreceptor tissue are grouped under the term chemodectoma and include: angioma, hemangioendothelioma, and nonchromaffin paraganglioma.

Glomus bodies are microscopic structures in the adventitia of the jugular bulb, and are found near the jugular fossa and the middle ear. The glomus complex lies above the base of the skull in the tympanic bone.

Glomus jugulare tumors originate in the basal portion of the petrous temporal bone and expand to destroy adjacent bone. The tumor extends into the internal and middle ear, and sometimes into the external auditory canal, where it may present as a polyp. Extension downward through the jugular foramen and involvement of nearby cranial nerves is a late complication.

The predominant symptoms and signs of glomus jugulare tumors in this series are: diminished hearing; vertigo; hoarseness; cranial nerve involvement; polyp in the external auditory canal; and bulging of the tympanic membrane.

Three of the cases of chemodectoma of the carotid body presented with a large mass in the neck. These tumors originate near the bifurcation of the common carotid artery.

The ages of the patients in this series varied from 38 to 78 years, with the majority being between 55 and 73 years. The mean duration of symptoms was 59.5 months for glomus jugulare tumors, and 22.5 months for carotid body tumors.

All of the cases of chemodectoma, except 1, were treated by radiotherapy. The majority of the patients received megavoltage irradiation with x-rays generated at 4 mev. Dosage ranged from 4,000–6,000 rads delivered in 24–43 days.

Six of the 25 patients died. One patient developed distant metastasis.

The report includes details of each case, drawings demonstrating the treatment fields of irradiation, and a review of the literature of this rare tumor.—*Paul M. Dassel, M.D.*

Abdomen

Sellink, J. L. Radiologic examination of the small intestine by duodenal intubation. *Acta radiol.* (Diag.), May, 1974, *15*, 318–332. (From: The Department of Radiology, University Hospital, Leiden, Holland.)

Infusion of barium through a tube is recommended for the routine examination of the small bowel.

The extended Bilbao tube, a modification of the Bilbao-Dotter tube (*Radiology*, 1967, *89*, p. 438), is inserted into the duodenum until the ligament of Treitz area is approached. Usually the tube can be successfully introduced in a few minutes. A volume of 500 to 600 ml. of stable barium suspension is routinely infused in 5 to 6 minutes.

The head of the barium column entered the cecum within 6 minutes in 33 per cent of the cases. In another 33 per cent of the patients the contrast medium entered the cecum several minutes later, or after a supplementary dosage of 300 ml. of either barium or water. In the remaining cases there was retarded transit, and a supplemental volume of 600 ml. of contrast medium was infused. The maximum volume given was 1,200 ml. of barium and an additional equal volume of water. The cecum, or the site

of obstruction, was usually reached within 1 hour. The largest volumes infused were in cases of paralytic ileus, obstruction, scleroderma, and similar conditions.

The specific gravity of the contrast medium is important. The normal patient can be best examined with a barium mixture having a specific gravity of 1.25. The specific gravity should be increased to 1.3 for an obese patient, reduced to 1.2 for a thin patient, and reduced further to 1.15 for young children.

Preparation of the patient for the small bowel examination is considered important. The author suggests a low residue diet for 24 hours with the last meal fat free. Medication reducing peristalsis is withheld. The colon is cleansed by the oral route. No preparatory enemas are given.

This method of small bowel examination greatly reduces the possibility of flocculation of barium by allowing the rapid filling of the entire small intestine. Once flocculation has developed, anatomic true representation of the intestinal lumen is no longer possible. Malabsorption and inflammatory disease of the bowel increase the rapidity of deterioration of the contrast medium and often delay transit.

All loops of small bowel are distended by the rapidly infused large volume of contrast medium. Small irregularities in the mucosa are less likely to be missed when examined in the well-filled state, rather than in loops that are partially contracted.

The colon may be examined following the small bowel study by flushing the small intestine with water, so that the barium mixture is advanced to the colon. Air may be injected either through the tube or by rectal insufflation for a double contrast study.

The author has examined over 1,500 patients by this method during a period of 3 years.—*Paul M. Dassel, M.D.*

Holder, Lawrence E., and Schneider, Harold J. Spigelian hernias: anatomy and roentgenographic manifestations. *Radiology*, Aug., 1974, *112*, 309–313. (Address: Lawrence E. Holder, M.D., Cincinnati General Hospital, Cincinnati, Ohio 45229.)

The authors concisely discuss the anatomy and radiographic findings of this form of lateral ventral hernia which may present as intermittent abdominal pain, "vanishing masses," or symptoms suggesting acute bowel obstruction. Experience with 10 patients—5 of whom had radiologic examinations—showed that 5 (50 per cent) had incarcerations.

The key radiographic findings are: air or contrast filled bowel seen laterally outside the confines of the peritoneal cavity; the "beak sign" of hernia; the sharp constriction of the proximal herniated loop; and the intermittent nature of the hernia. The contents of the hernia sac may include almost any structure or organ located within the peritoneum.—*W. I. Dittman, M.D.*

Erasmie, U., and Ringertz, H. G. Abdominal dimensions and thickness of the subcutaneous fat in the fetus. *Acta radiol.* (Diag.), May, 1974, *15*, 257–264. (From: The Department of Diagnostic Radiology, Karolinska Sjukhuset, 10401 Stockholm, Sweden.)

The thickness of subcutaneous fetal fat is an indication of fetal maturity.

Fetal weight can be assessed by roentgen measurement of the abdominal diameter (A), and the lumbar vertebral length (V). The quotient A/V was evaluated in the fetus of normal and of diabetic mothers.

A detailed description of the method, and an analysis of the measurements obtained are provided.

The authors conclude that there is no significant difference in thickness of subcutaneous fat, of the abdominal diameter, and of the lumbar vertebral length between the fetus of normal and diabetic mothers.—*Paul M. Dassel, M.D.*

Falk, Henry, Creech, John L., Jr., Heath, Clark W., Jr., Johnson, Maurice N., and Key, Marcus M. Hepatic disease among workers at a vinyl chloride polymerization plant. *J.A.M.A.*, Oct., 1974, *230*, 59–63. (Address: Henry Falk, M.D., Cancer and Birth Defects Division, Bureau of Epidemiology, Center for Disease Control, 1600 Clifton Road, Atlanta, Ga. 30333.)

Seven cases of angiosarcoma of the liver and 4 of nonmalignant liver disease were found in the last 10 years among employees at a single vinyl chloride polymerization plant.

In this plant, vinyl chloride monomer is placed in polymerization vats with other chemicals and the polymerized material is then concentrated, dried and packaged as 3 products; resin, paste and latex. The greatest employee exposure is after the polymerization process, when the reactors are cleaned and retained vinyl chloride monomer is released. Initially, cleaning was done manually, but new methods were introduced to prevent acro-osteolysis which may occur in polyvinyl chloride workers.

In the last 10 years 7 cases of angiosarcoma were diagnosed, 3 first recognized at autopsies, and 4 additional cases of fibrosis of the liver, biopsy proven. These were all in polyvinyl chloride workers and none in the remainder of plant employees.

Symptoms varied considerably with mild to severe pain, and liver function tests were inconsistent. The 7 men with angiosarcoma had worked at the plant an average of 18 years and all had had some employment cleaning tanks. In the 3 cases first diagnosed

at autopsies, prior biopsies showed portal fibrosis, sinusoidal dilatation and atypical sinusoidal lining cells. The 4 patients with nonmalignant hepatic disease had worked an average of 20 years and only 1 had never cleaned tanks. All 4 had some degree of hepatic fibrosis; histologically, this was similar to the changes noted in the angiosarcoma patients. No patients had acrolysis and none had hepatitis.

Regardless of mechanism, these studies show that relatively high levels of vinyl chloride monomer exposure and a long time interval are involved, but this product or a derived metabolite is apparently responsible for angiosarcoma of the liver and a nonmalignant fibrosis.—*Martha Mottram, M.D.*

GENITOURINARY SYSTEM

SHERWOOD, THOMAS, DOYLE, F. H., BOULTON-JONES, M., JOEKES, A. M., PETERS, D. K., and SISSONS, P. The intravenous urogram in acute renal failure. *Brit. J. Radiol.*, July, 1974, *47*, 368–372. (From: Departments of Radiology and Medicine, Institute of Urology with St. Peter's Hospitals, London, W.C.2, and Royal Postgraduate Medical School with Hammersmith Hospital, London, W.12, England.)

High dose intravenous urography has been shown to be safe and to yield valuable information in the presence of oliguric acute renal failure. The relationship between the density and duration of a nephrogram is particularly important in evaluation of recoverable acute renal failure, as in acute tubular necrosis.

In a series of 50 patients with acute renal failure and oliguria, the roentgenograms were classified into 4 groups: no nephrogram at any time; a questionable nephrogram; a distinct nephrogram, appearing early, and persisting without large density change; and a nephrogram of increasing density.

In all 4 patients in this series, in whom urinary tract obstruction existed, the situation was revealed by the study, which included a 24 hour roentgenogram. Other causes of an abnormal, long lasting nephrogram, in particular, acute ureteric obstruction, hypotension, and renal ischemia, were associated with a pattern of increasing nephrogram density.

Most patients with uncomplicated acute renal failure due to acute tubular necrosis show an immediately dense nephrogram which usually does not change in density. In the few patients with this diagnosis in whom there was a feeble nephrogram, there were complicating factors, such as cortical necrosis, or a hematologic disorder, as well. In a small number of patients with uncomplicated acute tubular necrosis, the nephrogram unaccountably increased in density.

In 7 patients a dense nephrogram was encountered in the presence of underlying disease other than reversible acute tubular necrosis. Clinical, microscopic, and radioisotope investigations satisfactorily differentiated these from the patients with acute tubular necrosis.

There is no indication that any of these patients was harmed by the high dose intravenous urography. —*E. Frederick Lang, M.D.*

SHAWKET, TALAL N., and AL-WAIDH, MACKI. Hydatid cysts of the kidney: simulating similar kidney lesions. *Brit. J. Urol.*, Aug., 1974, *46*, 371–376. (From: Department of Surgery, Genitourinary Service, Medical Center, Baghdad Medical College, Baghdad, Iraq.)

The Medical Center College in Baghdad had 1,346 patients with hydatid disease in the last 10 years, 57 of which were in the kidney. The more usual sites were liver, lungs and bones.

General symptoms are rare; loss of strength, weight loss and eosinophilia with occasional urticaria. The definite diagnostic signs are hydatiduria, positive Weinberg and Casoni tests and a cyst demonstrated roentgenographically which may have a calcified margin.

Four detailed case reports indicate that all patients do not have the "typical" hydatid signs and tumor was the provisional diagnosis; one 7 year old girl had a huge mass replacing the upper and middle calyces; 3 other patients had partial calyceal filling only, but no cysts were identified. A fifth patient had renal colic and erosion of several of the right minor calyces. He was initially considered to have tuberculosis, but later passed cystic bodies in the urine.

The reproductions of the pyelograms are only fair, but there are photographs of the specimens. Angiography should prove of value in future cases to differentiate cyst from tumor.—*Martha Mottram, M.D.*

CARSWELL, J. WILSON. Intraperitoneal rupture of the bladder. *Brit. J. Urol.*, Aug., 1974, *46*, 425–429. (From: Department of Surgery, Mulago Hospital, Kampala, Uganda.)

A report from Uganda describes 11 cases of intraperitoneal rupture of the bladder; 1 patient also had tear of the posterior urethra. In 7 patients there was a blow to the abdomen and 4 were pedestrians struck by cars.

All patients had lower abdominal pain and failure to urinate associated with abdominal tenderness; no fever. Several of the catheterized patients had a little blood-stained urine. Treatment was delayed in 1 patient who had 1,000 cc. on catheterization on each of 4 days, which was later shown to be intraperitoneal urine from a large rupture. Two patients had blood-stained urine on peritoneal tap.

There were delays of 1 to 4 days prior to surgery in 5 instances. There were no deaths. One patient had postoperative infection. At surgery, there was no significant peritoneal inflammation and the author suggests that the high urinary pH of Africans in Kampala may inhibit the growth of *E. coli*.—*Martha Mottram, M.D.*

Barrilero, A. Escudero, Borruel, J. L. Sebastián, and Martínez-Piñeiro, J. A. Pseudotumeurs rénales. (Renal pseudotumors.) *J. d'urol. et néphrol.*, June, 1974, *80*, 495–500. (From: Clinica La Paz, Servicio de Urologia, Facultad autonoma de Medicina, Madrid, Spain.)

The congenital hypertrophy of the columns of Bertin which is at times demonstrable during an intravenous urography is not considered a pathologic entity and should be recognized as such in the differential diagnosis between small renal adenocarcinomas.

This anomaly, which is more frequently observed in a bifid kidney, is in particular found between the superior and middle calyces which are slightly compressed, displaced and elongated. Nephrotomograms show roundish, well defined dense intraparenchymal masses, and King *et al.* (1968) pointed out that these shadows are surrounded, at times partially, by a radiolucent ring which is thought to be produced by adjacent fat.

It is selective renal angiography which, in demonstrating a normal caliber of the renal artery and its branches, an absence of newly formed vessels and only a smooth arcuate compression effect on the interlobar arterial branches, confirms the presence of the columns of Bertin.

Three cases which presented this renal anatomic variation are reported in detail.—*A. F. Govoni, M.D.*

Hutton, Ian M., and Green, N. Alan. High-dose delayed urogram in the detection of the occult ectopic ureter. *Brit. J. Urol.*, June, 1974, *46*, 289–294. (Address: Dr. Ian M. Hutton, Senior Surgical Registrar, Hammersmith Hospital and Postgraduate Medical School, London, England.)

Four cases of ureteral ectopy are reported and the use of high-dose urography with delayed filming is emphasized. The first case was a classical presentation, the second less usual, and the last 2 exceptional, but similar. The classical presentation of ureteral ectopy is that of urinary incontinence from an early age between episodes of normal voiding. In the second patient a diagnosis was not made until the patient was 19 years old at which time utilization of a high-dose urogram showed initially a lateral displacement of the "normal" ureter on the affected side, implying the presence of a dilated ectopic ureter; in a delayed radiographic tomogram series the abnormal left upper renal pelvicalyceal structure was opacified. The third case demonstrated a bilateral complete duplication with bilateral ectopy and utilization of high-dose urography was again useful in demonstrating a definite left-sided saccular opacity above an otherwise normal looking left kidney.

The "drooping flower" appearance is classical but not invariable and was present in only 1 of the 6 ectopic renal segments presented in this paper. Lateral displacement of the ureter draining the normal renal segment, particularly at its lower part by a non-visualized ectopic ureter, may be seen. Other inconstant signs are: widening of the area between the upper renal outline and the uppermost secreting calyx; and lateral displacement of the normally secreting renal segment. Over-all, only 1 of 6 ectopic ureteric openings was detected without some difficulty or delay. The authors used Conray 325 with the periods of delayed radiography varying from 3 to 24 hours. Five of 6 abnormal kidneys with ectopic segments eventually secreted and concentrated enough contrast material for adequate demonstration on conventional radiography without tomography.

Use of ureteropyelograms shows that the ectopic renal segments may appear larger in size than on delayed urograms because distensibility of segments occurs more readily. However, high-dose delayed urography may be a valuable procedure in demonstrating a poorly secreting superior segment.—*Lionel W. Young, M.D.*

Corinaldesi, Alberto, and Roversi, Rigoantonio. L'arteriografia selettiva nello studio delle surrenali. (Selective arteriography in the study of the adrenals.) *Radiol. med.*, March, 1974, *60*, 193–208. (Address: Dr. Alberto Corinaldesi, Istituto di Radiologia dell'Università, 9 via Massarenti, I-40138 Bologna, Italy.)

Selective angiography of the adrenal arteries has been the object of study by several authors. While a few, among them Lagergren (1967) and Joffre (1972), are of the opinion that this angiographic study not only fails to offer great diagnostic advantages, but also is not devoid of complications, others, such as Rossi *et al.* (1966), Kahn and Nickrosz (1967), and Alfidi *et al.* (1969) consider selective adrenal angiography an important diagnostic procedure and have not found a greater incidence of complications.

The authors have examined by selective adrenalography 30 patients in whom an adrenal pathologic process was suspected and have in particular evaluated the findings observed in 5 cases of pheochromocytoma, and 1 case each of adenoma of Conn and

of adrenal cortical hyperplasia. All cases were proved at surgery and the diagnosis confirmed histologically.

The procedure was the following: 1st stage, abdominal aortography by catheterization; 2nd stage, selective renal angiography; 3rd stage, selective angiography of the middle adrenal and inferior phrenic arteries, if possible bilaterally. The 2nd and 3rd stages were performed whether or not the aortograms were normal. The amount of contrast medium injected for the selective adrenalograms was between 2 and 4 cc., which was injected manually. The angiograms were exposed at 2 per second per 3 seconds and then at 1 angiogram per 4 seconds.

The observations presented by the authors can be briefly summarized as follows: (1) the procedure was well tolerated and technically feasible in the majority of cases; (2) the selective injection of the contrast medium resulted in a noticeable improvement of the quality of the angiograms and, therefore, of the diagnostic information obtainable; (3) in the 3 cases of benign pheochromocytoma and in the 2 of malignant pheochromoblastoma, selective adrenalography proved to be of greater diagnostic importance than selective renal angiography or aortography; (4) the visualization of an adrenal adenoma and of adrenal hyperplasia was possible, although not always, by selective adrenal angiography; (5) an enlargement of the adrenal gland was the only finding demonstrable in adrenal hyperplasia because the arterial and venous circulations were normal or minimally altered; and (6) the demonstration of an adenoma depended on its size, smaller ones could be easily missed even by this method. In their case of adenoma of Conn the adrenal gland appeared enlarged but with a normal vascular pattern, as was also found by Alfidi *et al.* (1969).

Numerous reproductions of the adrenal angiograms accompany the article.—*A. F. Govoni, M.D.*

Nervous System

Nyul-Tóth, P., and Joós, M. Über die Wirbelmanifestation der fibrösen Dysplasie. (Concerning the vertebral manifestation of fibrous dysplasia.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, June, 1974, *120*, 744–747. (Address: Dr. P. Nyul-Tóth, Leiter der Röntgen-Abteilung, H-1528, Budapest, Szanatorium Utca 2, XII./Ungarn.)

Vertebral manifestations of fibrous dysplasia are very uncommon. Only 38 cases have so far been described but poorly documented. An additional case is now reported.

The patient, a 26 year old man, presented with vague backache and a slight gibbus of the upper lumbar region, also a slight left convex scoliosis of the lower thoracic spine. Roentgenograms showed a pancake-type flattening of the second and third lumbar bodies which protruded anteriorly and bilaterally. The second lumbar body presented a concavity of its upper plate and the third one an anterior wedging. There was marked disk thinning from L1 and L4 and a spur at the lower border of the first lumbar body anteriorly contiguous with the protruding second lumbar body.

The bony substance of the affected bodies was diminished and presented an irregular contour. Large radiolucencies were noted between sparse and thickened trabeculae. Of further interest was an expansile cystic transformation of the right tenth rib posteriorly. Various biopsies confirmed the diagnosis of fibrous dysplasia.

The disease usually commences in childhood and puberty and is characterized by a slow progress. When detected in adult life, it can usually be traced to an earlier onset. The blood chemistry is unremarkable except for a slight elevation of the serum alkaline phosphatase. Values of calcium and phosphorus in blood serum remain normal.

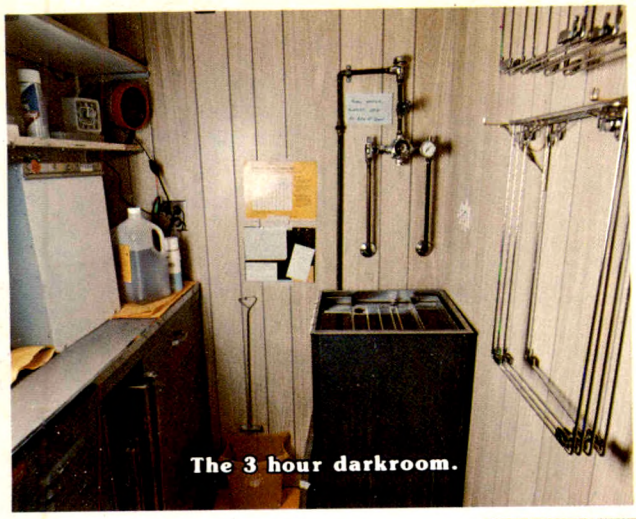
The differential diagnosis includes aneurysmal bone cyst, juvenile cyst, eosinophilic granuloma, von Recklinghausen's disease and osteitis deformans (Paget).—*Ernest Kraft, M.D.*

Kardjiev, Veliko, Symeonov, Andrei, and Chankov, Ivan. Etiology, pathogenesis, and prevention of spinal cord lesions in selective angiography of the bronchial and intercostal arteries. *Radiology*, July, 1974, *112*, 81–83. (Address: Dr. Veliko Kardjiev, Center of Oncology, Medical Academy, Plovdivsko Pole No. 6, Sofia, Bulgaria.)

Following the introduction of contrast material into the right fifth intercostal artery, 5 patients demonstrated evidence of spinal cord lesions. All had at least paresis of one or both limbs. A variant blood supply of segments D_4-D_6 of the spinal cord, named the radiculomedullary artery which arises from the right fifth intercostal artery, was the anatomic reason for finding the lesion in only 5 out of 28 patients.

The severity of the lesion was secondary to the toxicity, quantity, and the pressure of injection of the agent.

Sixty subsequent patients in whom no injection was made into the right fifth intercostal artery had no similar complications.—*R. F. Kuhnhein, M.D.*



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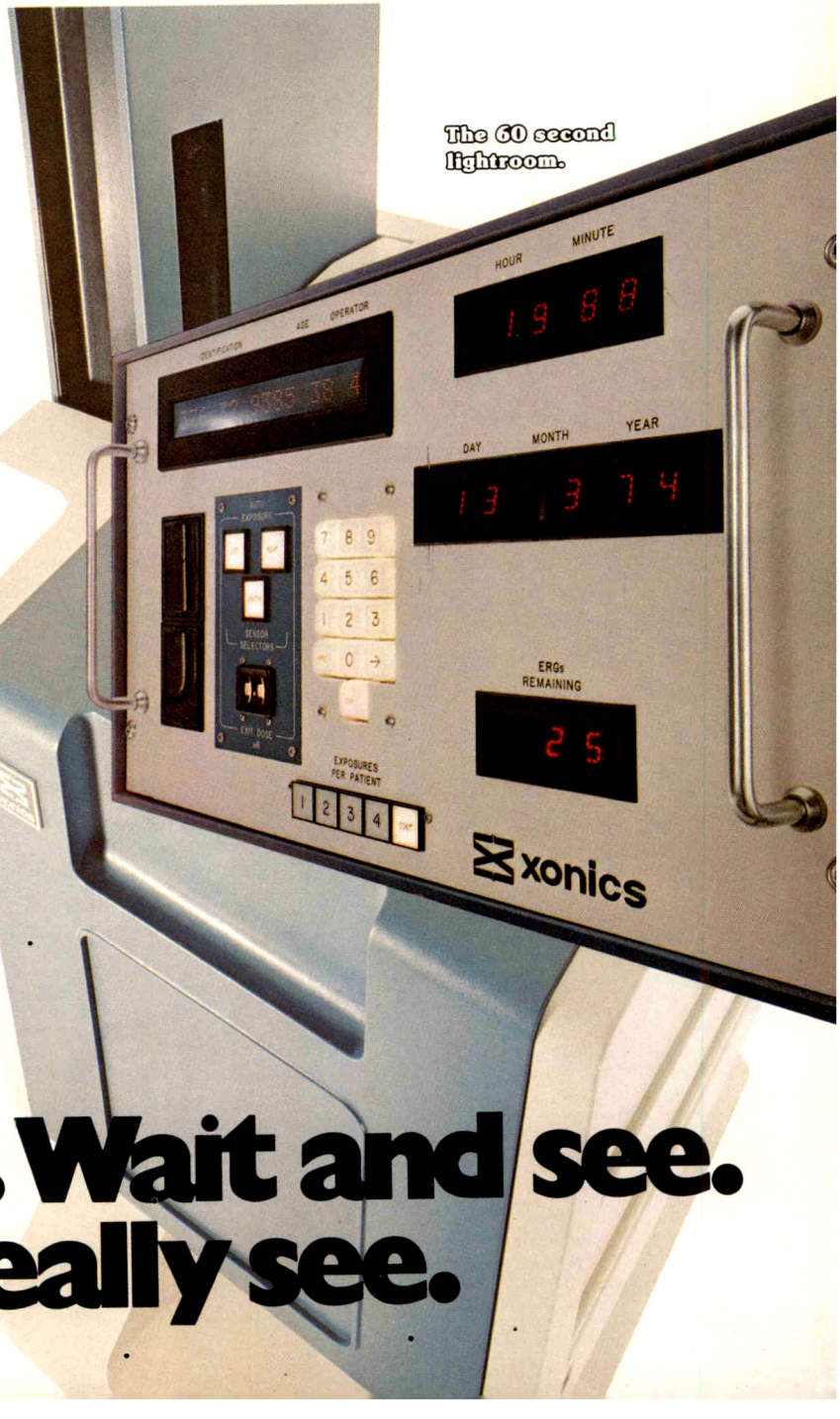

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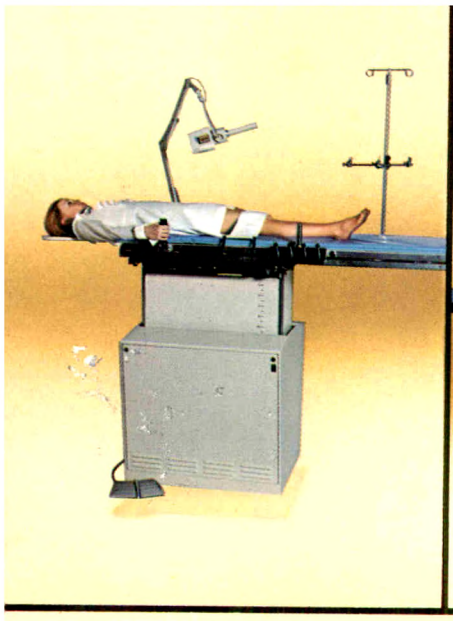
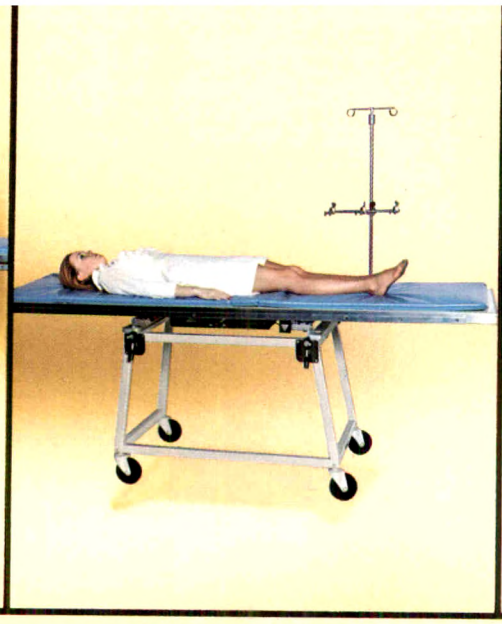


Neurovascular Configuration



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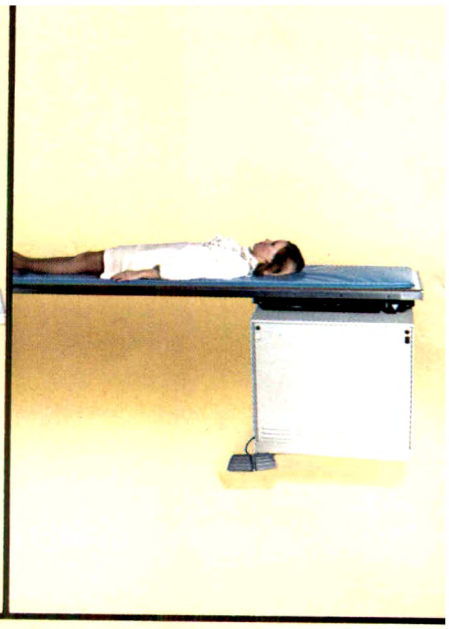

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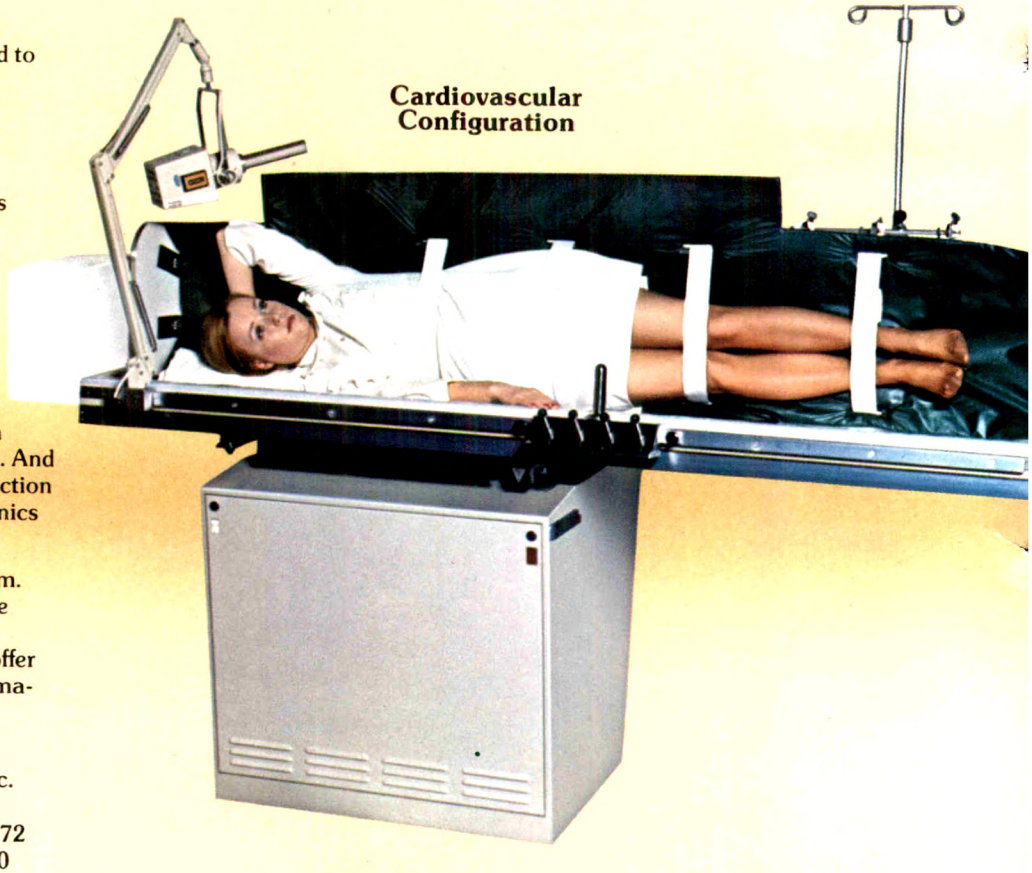

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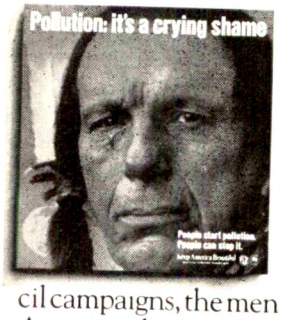

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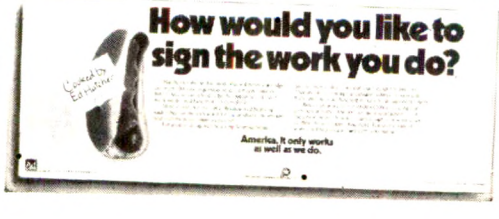

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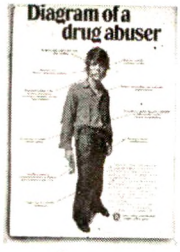

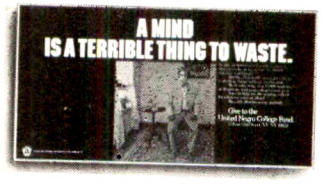

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THE BIOLOGICAL AND CLINICAL BASIS OF RADIOSENSITIVITY *edited by* **Milton Friedman,** *Instituto Regina Elena, Rome, Italy. (35 Contributors)* Radiosensitivity, a factor which must be considered in the treatment of every tumor and in most radiobiological experiments, encompasses disruptive changes that occur at many levels. The wide variety of factors under study has resulted in a communication gap between the laboratory and clinical researchers. In order to reduce this gap expert investigators in different fields were asked to adapt their observations to the concepts of radiosensitivity and chemosensitivity. Questions considered are: At which biological level do major effects occur? Which are the most important factors influencing radiosensitivity? What are the differences between radiosensitivity and chemosensitivity? What clinically useful information can be derived from cell survival curves? Can the variation in sensitivity during each phase of the cell cycle be used to improve the ultimate radiation effect? Should its possible usefulness be explored further, or should it be abandoned? At the preclinical level, the lethal dose for each tumor is depicted from several viewpoints. Combined radiation and chemotherapy is evaluated not only for potential benefits, but also for possible disruption of efficient irradiation. The neglected field of dynamic radiation pathology, studied by examination with light and electron microscopy, of serial biopsy specimens is surveyed. Finally a detailed investigation is described, wherein the validity of a number of radiobiological laws are analyzed during the treatment of squamous cell carcinoma. A comprehensive and detailed index renders a vast amount of available information. *'74, 592 pp. (7 x 10), 373 il., 67 tables, $49.50*

RADIONUCLIDE SCANNING IN CYANOTIC HEART DISEASE *by* **Gary F. Gates,** *Memorial Hospital Medical Center and Earl and Loraine Miller Children's Hospital of Long Beach, California.* During past years nuclear medicine has undergone tremendous growth due to advances in radiopharmaceuticals and instrumentation. Use of short-lived radioisotopes such as technetium-99m and the scintillation camera allow for rapid performance of examinations with extremely low radiation dose to the patient. This monograph describes a new, unique application of nuclear medicine in the clinical management of children with cyanotic congenital heart disease. The procedure is fully described, the steps used in performing the examination outlined and possible pitfalls and sources of error presented. The calculation of results does not require sophisticated mathematics nor complicated computer analysis. Accuracy is assured by correlation with surgery or cardiac catheterization. Although this procedure has usefulness in many pediatric cardiopulmonary disorders, its application to the surgical patient is unique. Physiologic data, previously obtainable only by cardiac catheterization, can now be produced serially by an outpatient examination. This helps to fill the gap between chest radiography and cardiac catheterization and aids in the successful management of patients with cyanotic congenital heart disease. *'74, 114 pp., 88 il., 5 tables, $15.00*

THE FUNDAMENTALS OF RADIOLOGICAL SCIENCE *by* **John Hale,** *Hospital of the Univ. of Pennsylvania, Philadelphia.* The four basic fields of applied radiological science are radiotherapy, clinical nuclear medicine, diagnostic radiology and radiation safety physics. It is the aim of this textbook to present the basic body of scientific knowledge which is common to the specialty fields of applied radiological science. A student needs exposure to two different texts—one dealing with basic radiological physics and another more advanced book dealing with one of the four specialized areas. He must have this basic understanding of fundamental principles in order to continue to learn to assimilate new ideas and methods throughout his professional life. Directed toward first-year residents in radiology, this book will also be useful as a beginning text for physicists and engineers who are interested in radiological or health physics. After a review of the basic mathematics and physics essential in the study of radiological sciences has been presented a careful study is made of atomic and nuclear physics, the radiation field and the interaction of radiation with matter. Finally, the fundamentals of dosimetry are discussed. *'74, 356 pp., 172 il., 3 tables, $14.75*

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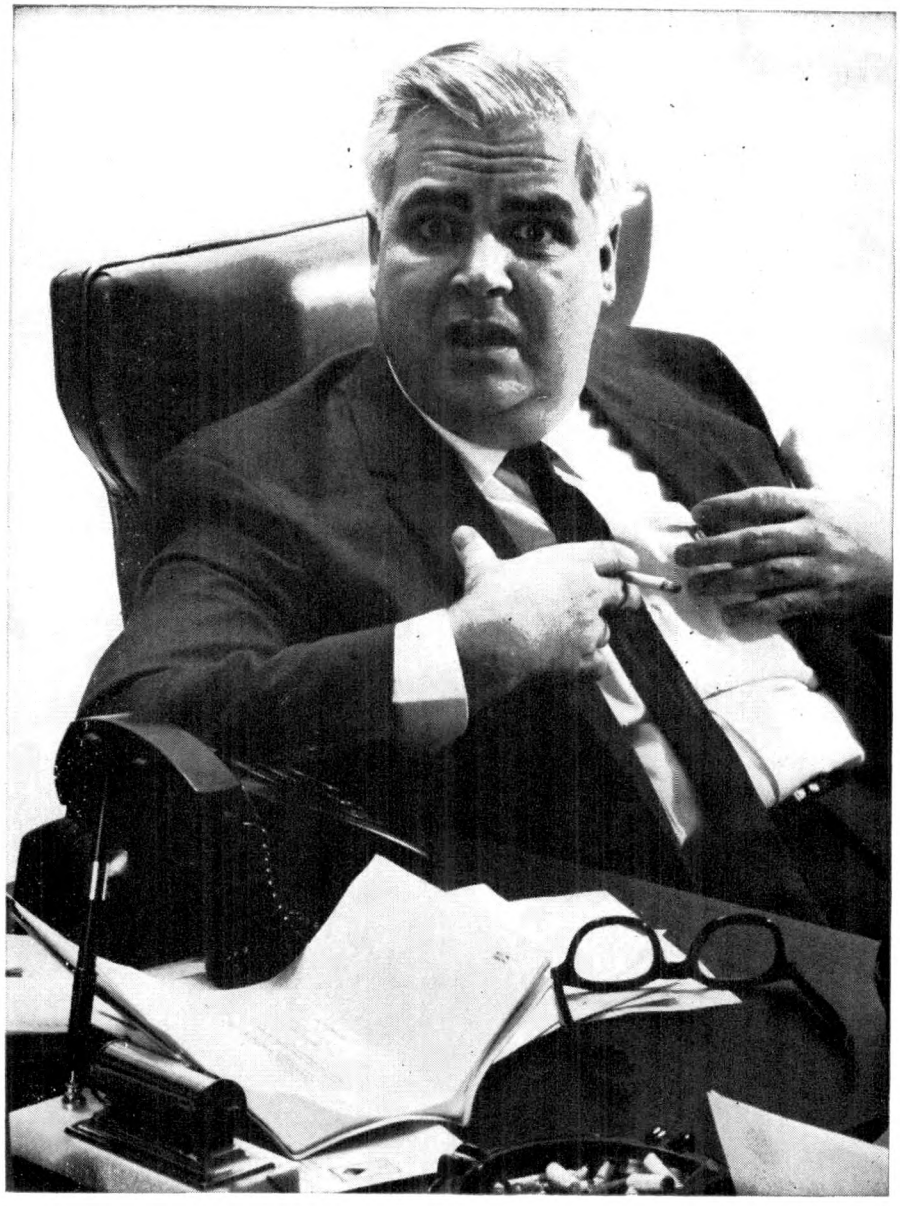

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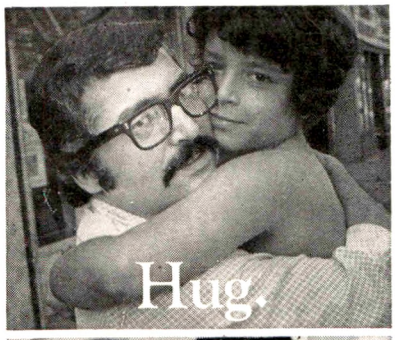

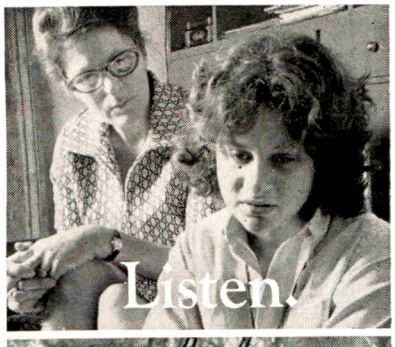

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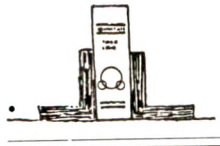

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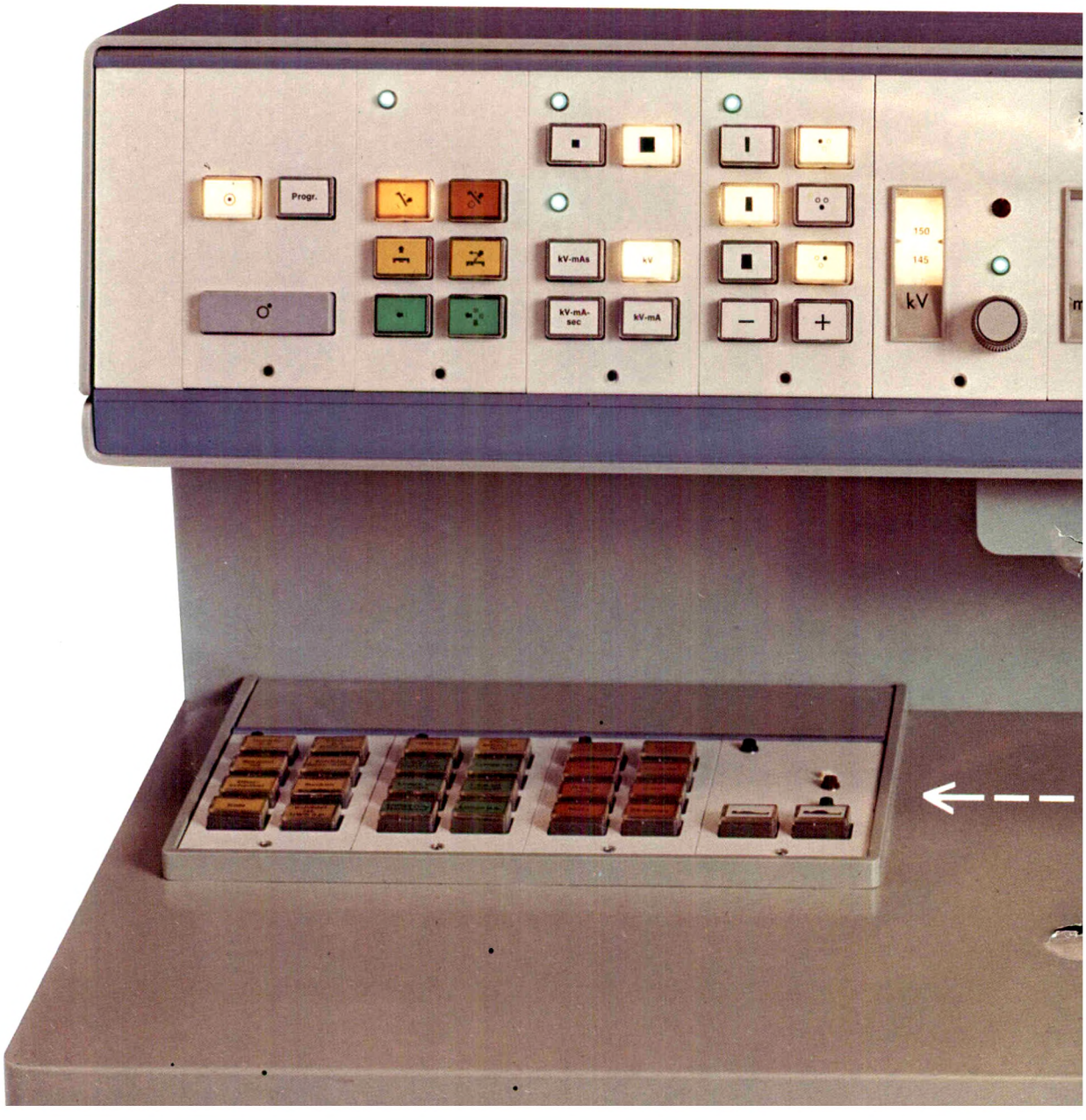

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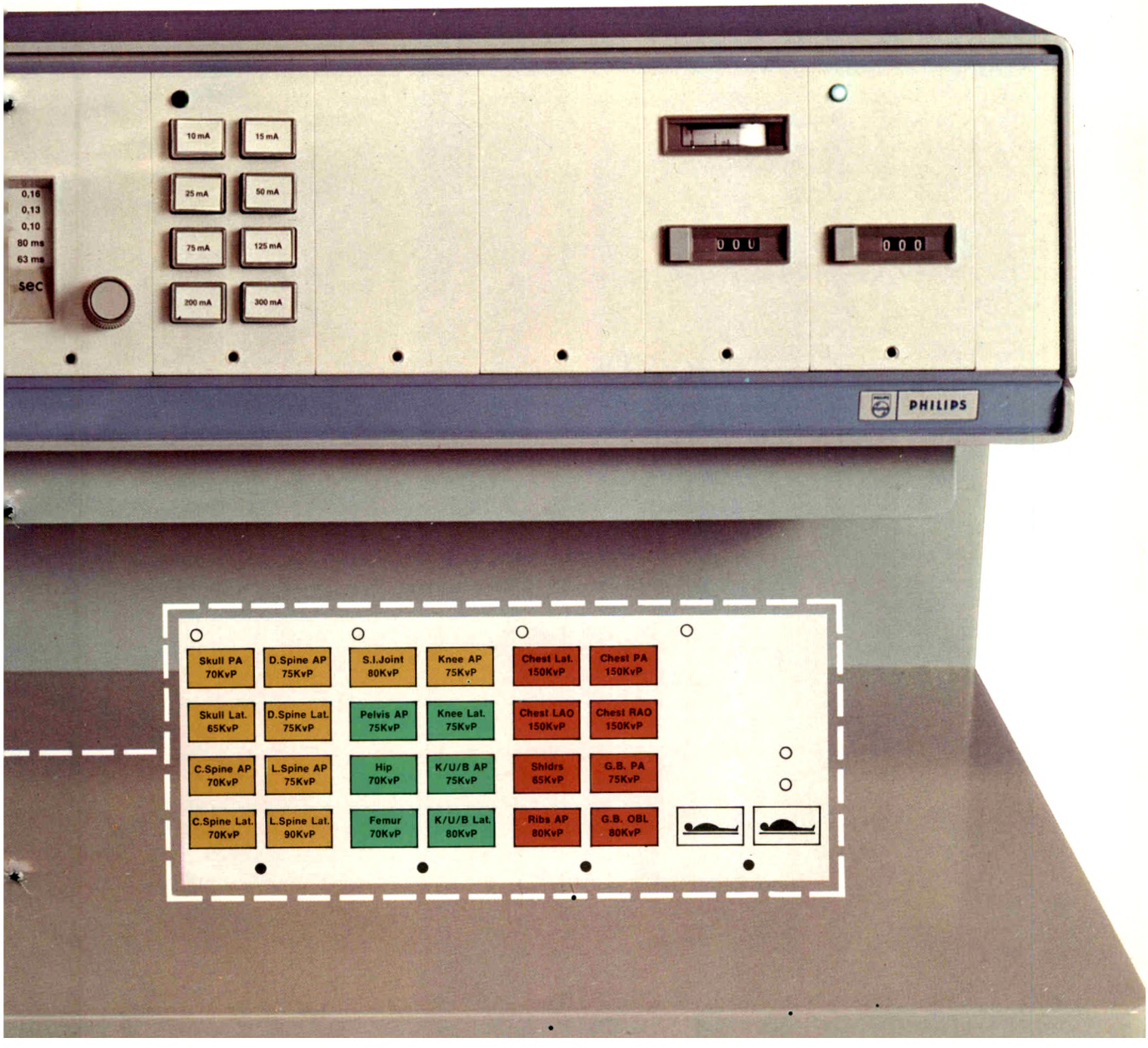

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ROENTGEN EXAMINATIONS IN ACUTE ABDOMINAL DISEASES (3rd Ed.) *by* **J. Frimann-Dahl,** *Ulleval Hospital, Oslo, Norway.* This new Third Edition is completely revised with 133 new black and white illustrations and two new color illustrations. Written for radiologists and students in diagnostic radiology, this book also serves as a guide and support for surgeons involved in this important and difficult emergency field. The book is primarily concerned with roentgen anatomy of the abdomen and unusual or normal variations. The diagnosis of the most important acute abdominal diseases is also covered including the following cases: the situation in which the actual lesion can be diagnosed on plain films only, the lesions which may be observed by repeat examinations, and emergency cases in which diagnosis must be made immediately. Acute abdominal diseases are among the most frequently referred cases. It is shown that roentgen examination is often decisive in the diagnosis and correct treatment which may save the life of the patient. Because there is often no opportunity for prolonged discussion of the cases, it is very important to have a book in which information can be sought concerning the actual case. The book begins with a discussion of procedure and technique including apparatus, quality of the films and use of contrast media. Normal findings are discussed for the peritoneal cavity, the development of peritoneum and alimentary canal and the roentgen anatomy of the abdomen. Normal variations of the roentgen anatomy of the intestinal tract and of the flank are reviewed along with the accumulation of gas and occurrence of fluid levels. Some abdominal diseases discussed are strangulating and obturating obstruction, mechanical obturation of the large bowel, congenital malformations causing intestinal obstruction, hernias, intussusception, volvulus and intestinal knot syndrome. Roentgen examinations are discussed for diagnosis in mesenteric thrombosis and strangulation, abdominal angina, acute regional enteritis, acute appendicitis, acute colitis, acute cholecystitis and pancreatitis, ulcer perforation of the stomach and duodenum, gynecological lesions and lesions in the urinary tract. Also discussed are rupture of the diaphragm, liver, spleen, kidney, stomach, duodenum, small intestine, colon and aneurysms. *'74, 632 pp., 614 il. (4 in full color), $29.50*

RADIOASSAY IN CLINICAL MEDICINE *edited by* **William T. Newton** *and* **Robert M. Donati,** *both of Washington Univ., St. Louis. (9 Contributors)* The editors of this volume have selected papers presenting in some detail the techniques and utilization of several useful radioassays, chosen to be representative of several classes of chemical compounds. Varied techniques in the field of radioassay and different types of compounds of clinical significance have been selected for presentation. Classification of these techniques and their clinical utility will lead to a better understanding of their role in clinical medicine today. The book is concerned with the techniques and use of radionuclides in the assay of chemical compounds of biologic interest. Techniques described include radioimmunoassay, inhibition assays, competitive protein binding assays and bioassays. Specific compounds of clinical interest also discussed include prostaglandins, digitalis, thyroid hormones, Vitamin B-12, long-acting thyroid stimulator and erythropoietin. *'74, 200 pp., 41 il., 24 tables, $11.75*

MODERN THIN-SECTION TOMOGRAPHY *edited by* **Arnold Berrett,** *New York Medical College, New York;* **Sam Brunner,** *Gentofte Hospital, Copenhagen, Denmark; and* **Galdino E. Valvassori,** *Univ. of Illinois, Chicago. Foreword by* **Solve Welin.** *(21 Contributors)* It is becoming increasingly important for the diagnostic radiologist to have working knowledge of the new developments and techniques in this field, the demands for which are increasing rapidly and appear likely to expand even further. This text, written by a number of prominent experts, clearly reflects the enormous advances diagnostic roentgenology has made in this special field. The contributors provide chapters on the history or tomography and physical principles involved, as well as a description of much of the equipment available. These chapters are followed by discussion of tomographic anatomy, technical factors, and clinical applications of the method in various parts of the body. Vital information is offered in the evaluation and diagnosis of otherwise obscure problems. *'73, 352 pp. (7 x 10), 496 il., 17 tables, $26.50*

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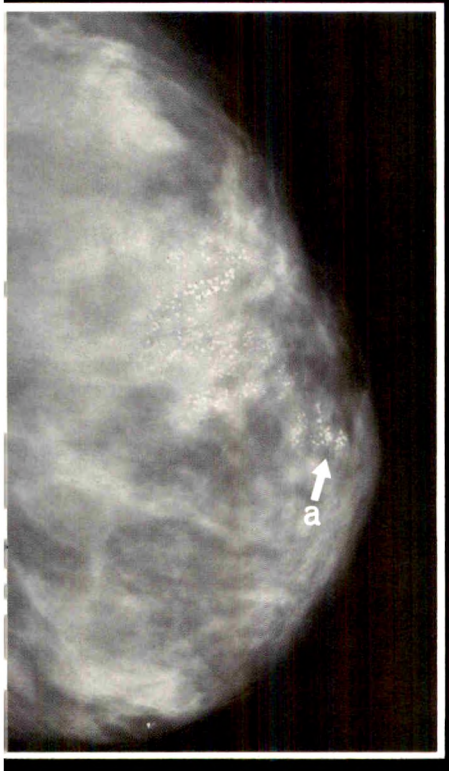

Figure I—Mixed Scirrhous and Papillary Comedocarcinoma Mediolateral mammogram reveals innumerable punctate calcifications throughout the upper half of the breast. Their differences in size, density, and shape are striking at (a). Note: The longer this breast is viewed the more calcifications one sees above and medial to those clustered at (a).

Figure II—Scirrhous Adenocarcinoma. Craniocaudal mammogram reveals diffuse fibrocystic disease plus a small cluster of punctate calcifications (arrow). The patient had a long history of fibrocystic disease for which the mammogram was made. No masses were suspected clinically. The granularity of the calcifications (arrow) plus their marked variability in size and shape seemed strong roentgen evidence in favor of cancer. An excisional biopsy revealed a grade 3 scirrhous adenocarcinoma 1.5 cm in diameter for which a radical mastectomy was performed. Three axillary lymph nodes revealed metastatic disease.

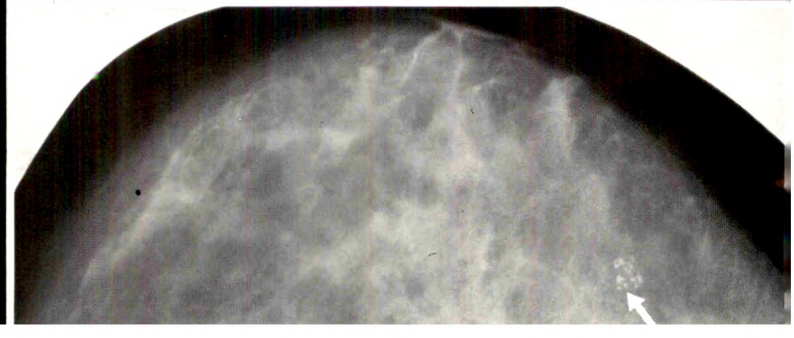

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Figure III—Scirrhous Adenocarcinoma.
Mediolateral mammogram reveals a host of tiny punctate calcifications (x) which seem to extend in linear fashion (arrow) toward irregular masses (a) in the upper part of the breast. Pathologically, many multicentric nodules of grade 4 scirrhous adenocarcinoma, varying from 0.2 to 3 cm in diameter, were scattered throughout the breast. Calcifications were present in several small carcinoma-filled ducts. It is noteworthy that none of the calcifications lie within the major mass (a); they seem to lie in a carcinoma-filled duct (arrow) or one of the multicentric nodules (x).

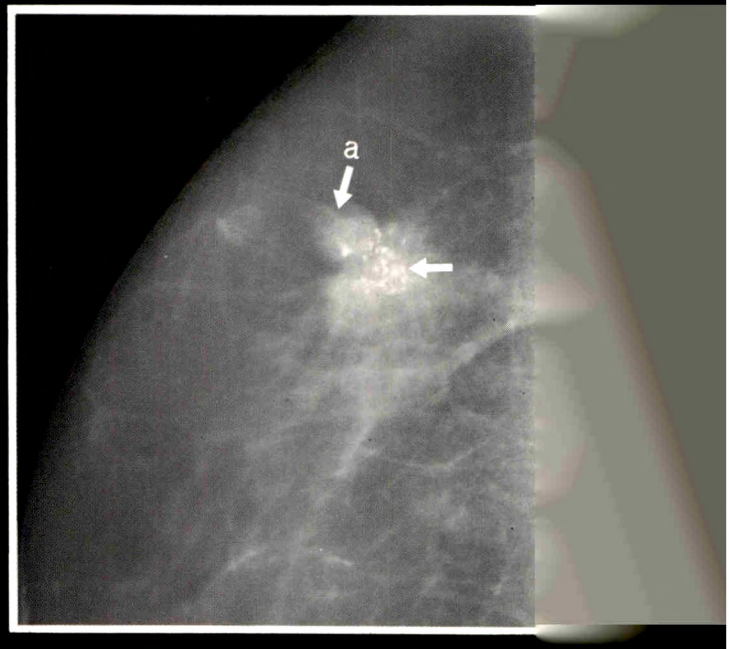

Figure IV—Infiltrating Comedocarcinoma.
A segment of a mediolateral mammogram reveals a discrete lesion within the center of which lies a cluster of tiny punctate calcifications (arrow) They vary markedly in size, configuration, and density. Radiographically, there was little doubt that this was cancer, despite the smooth, round and well-defined outline (a) of a portion of the tumor.

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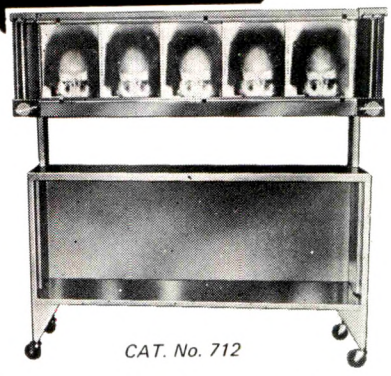

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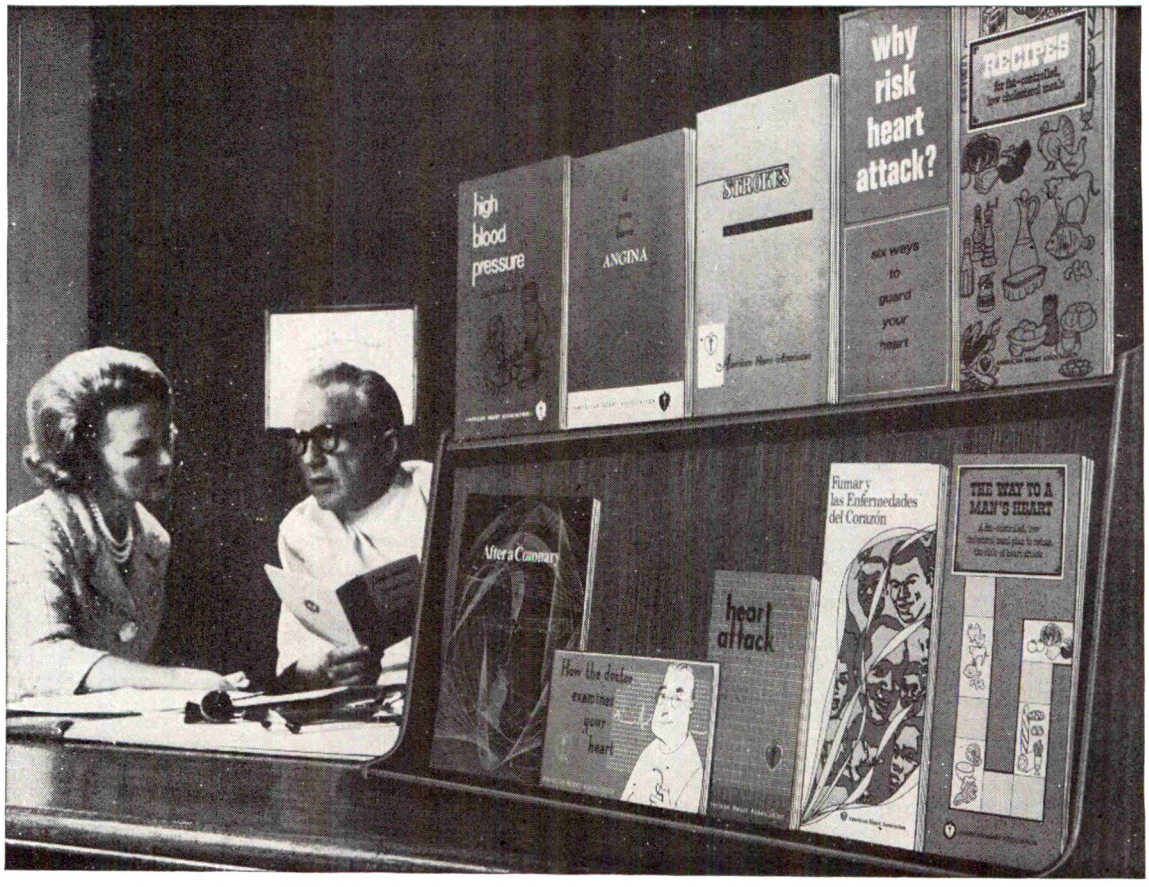

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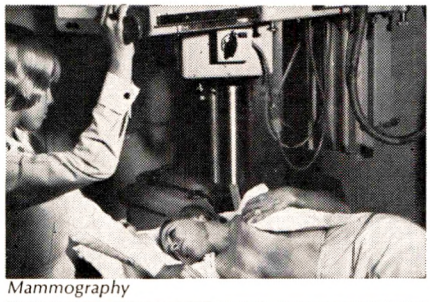
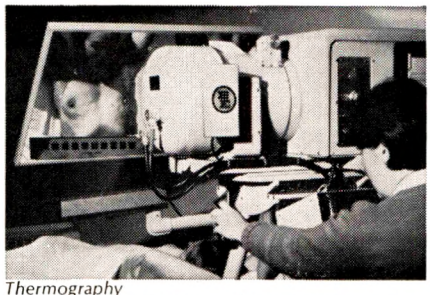


Mammography



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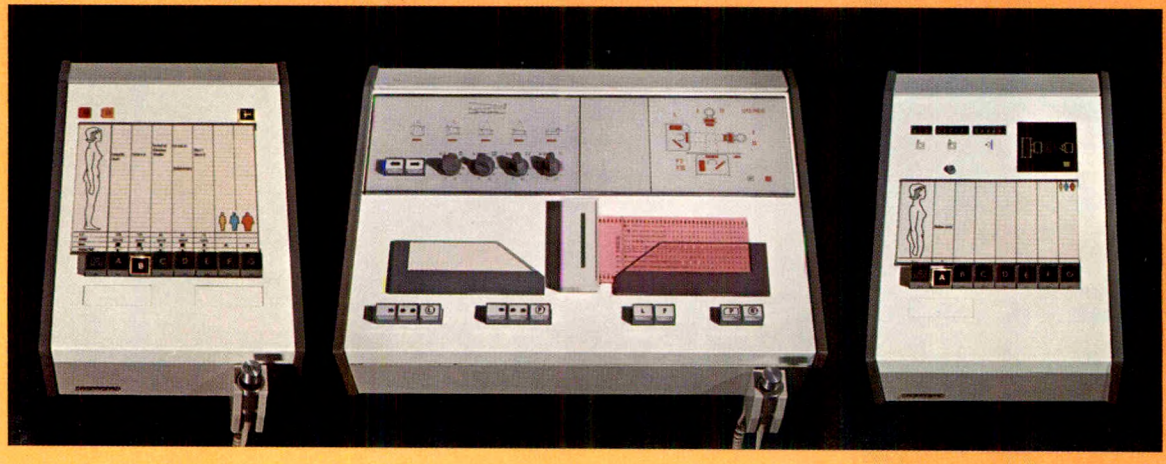

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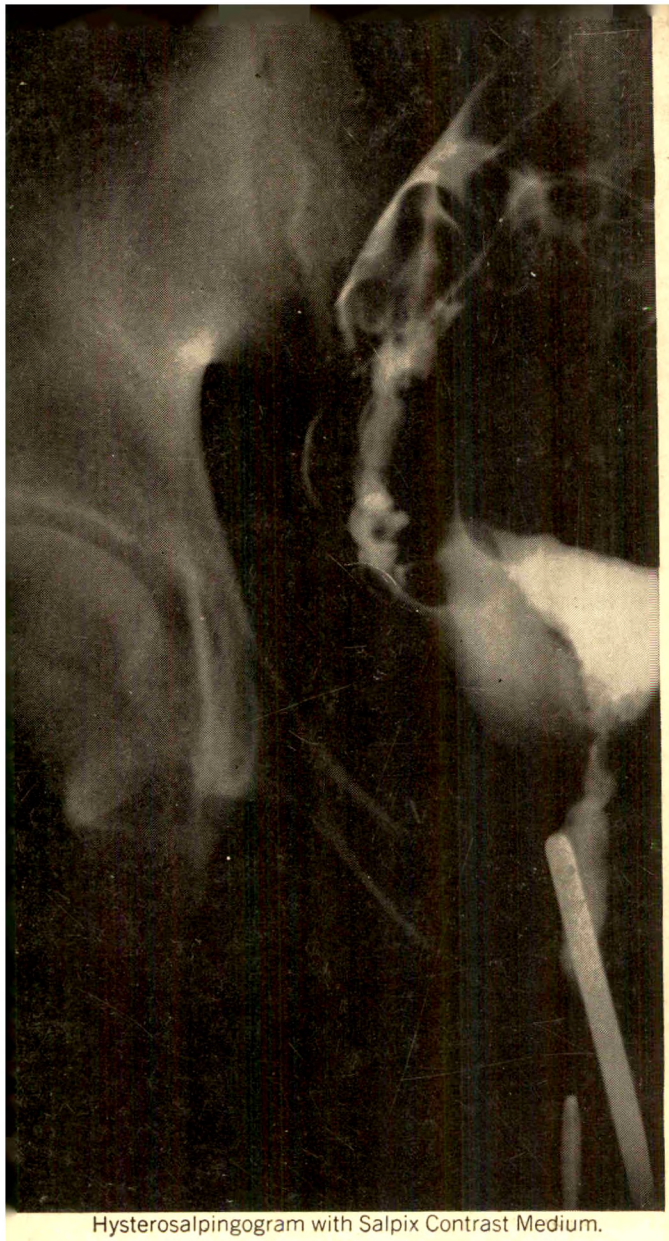

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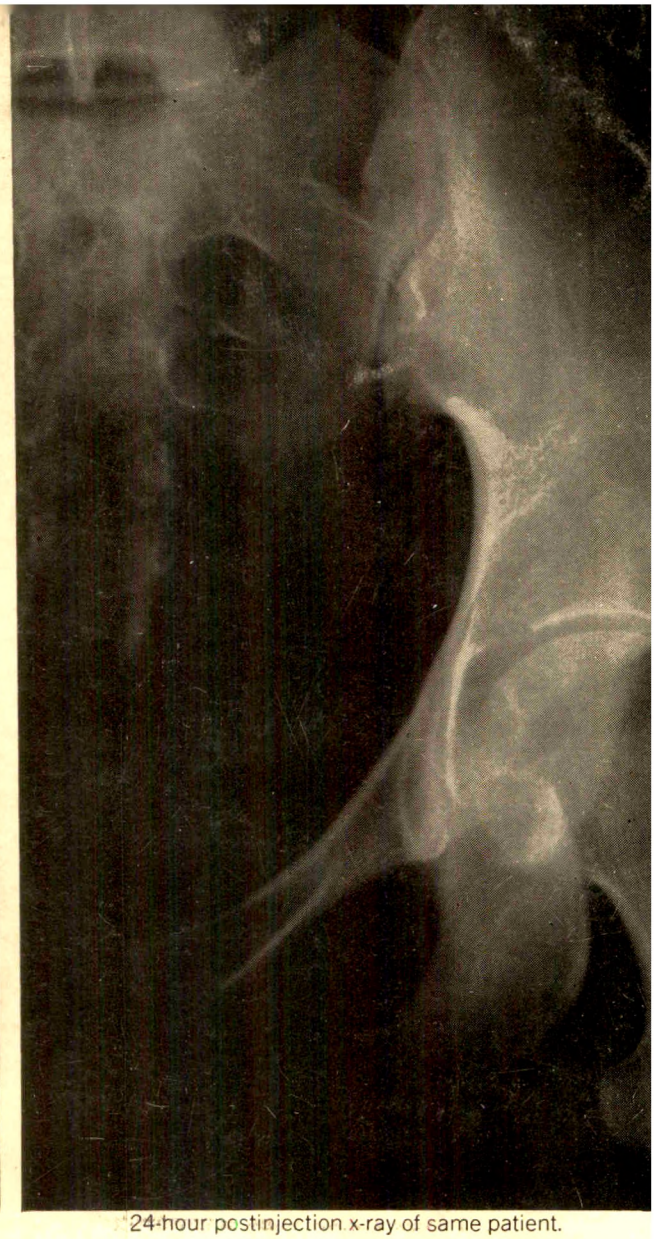

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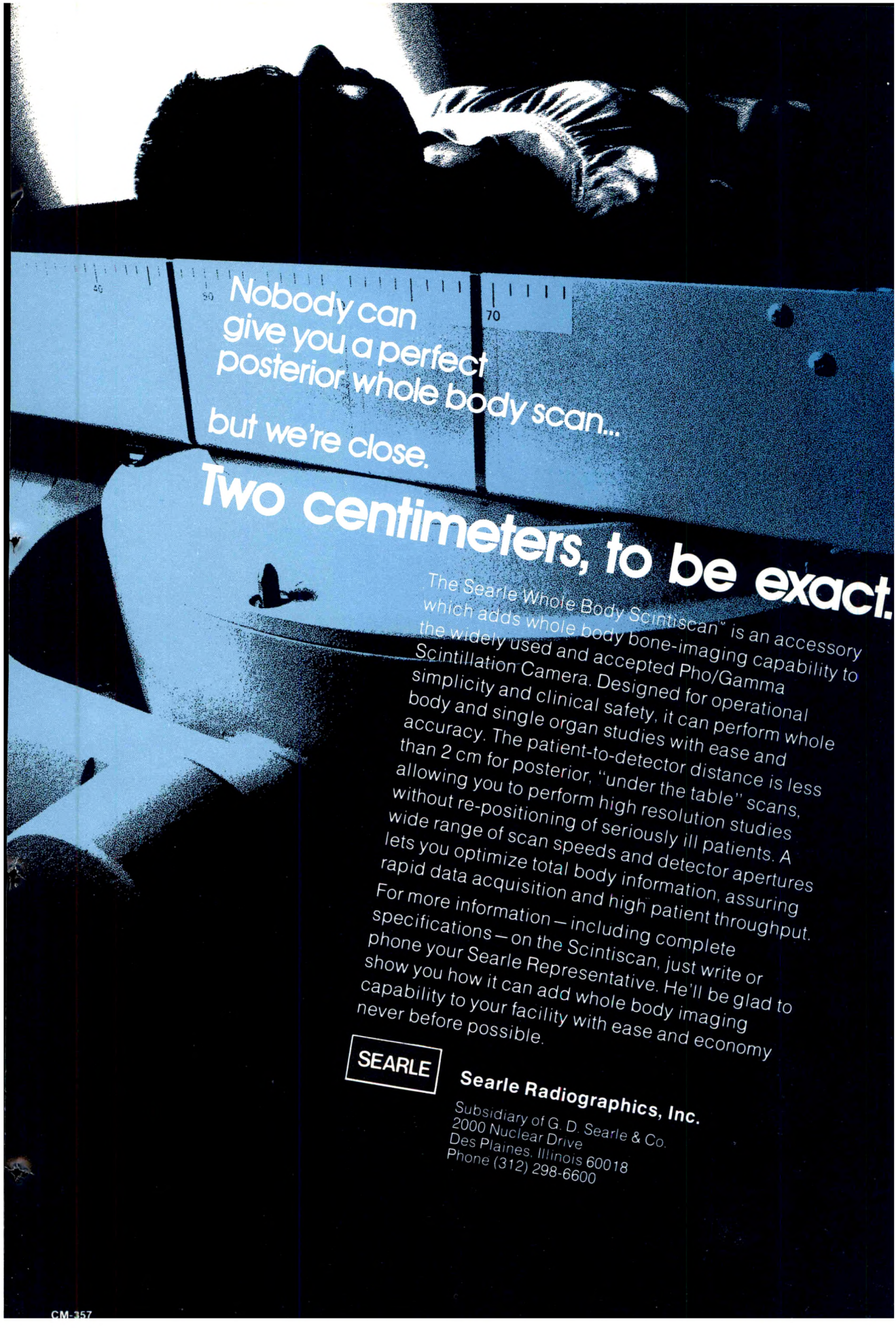

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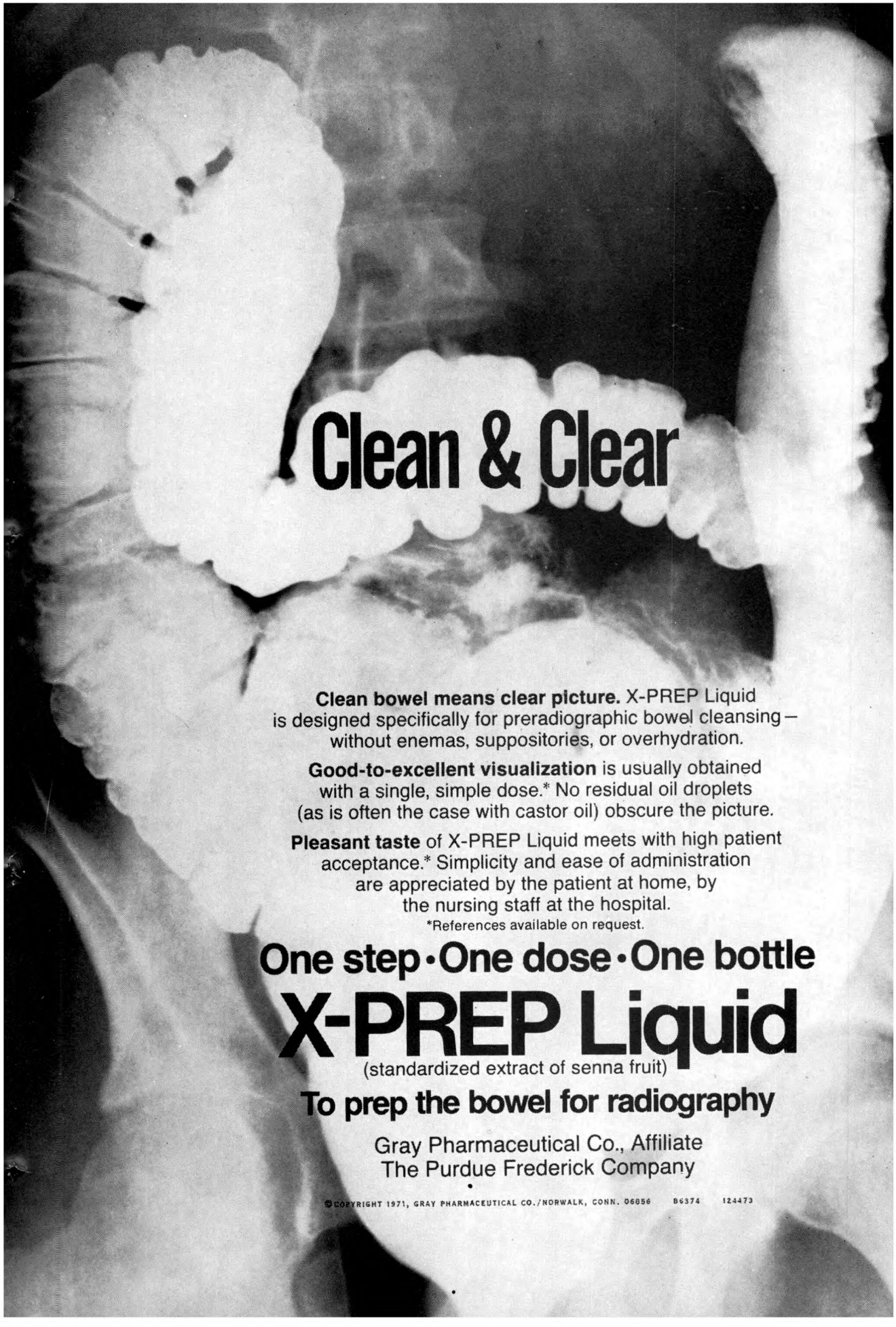

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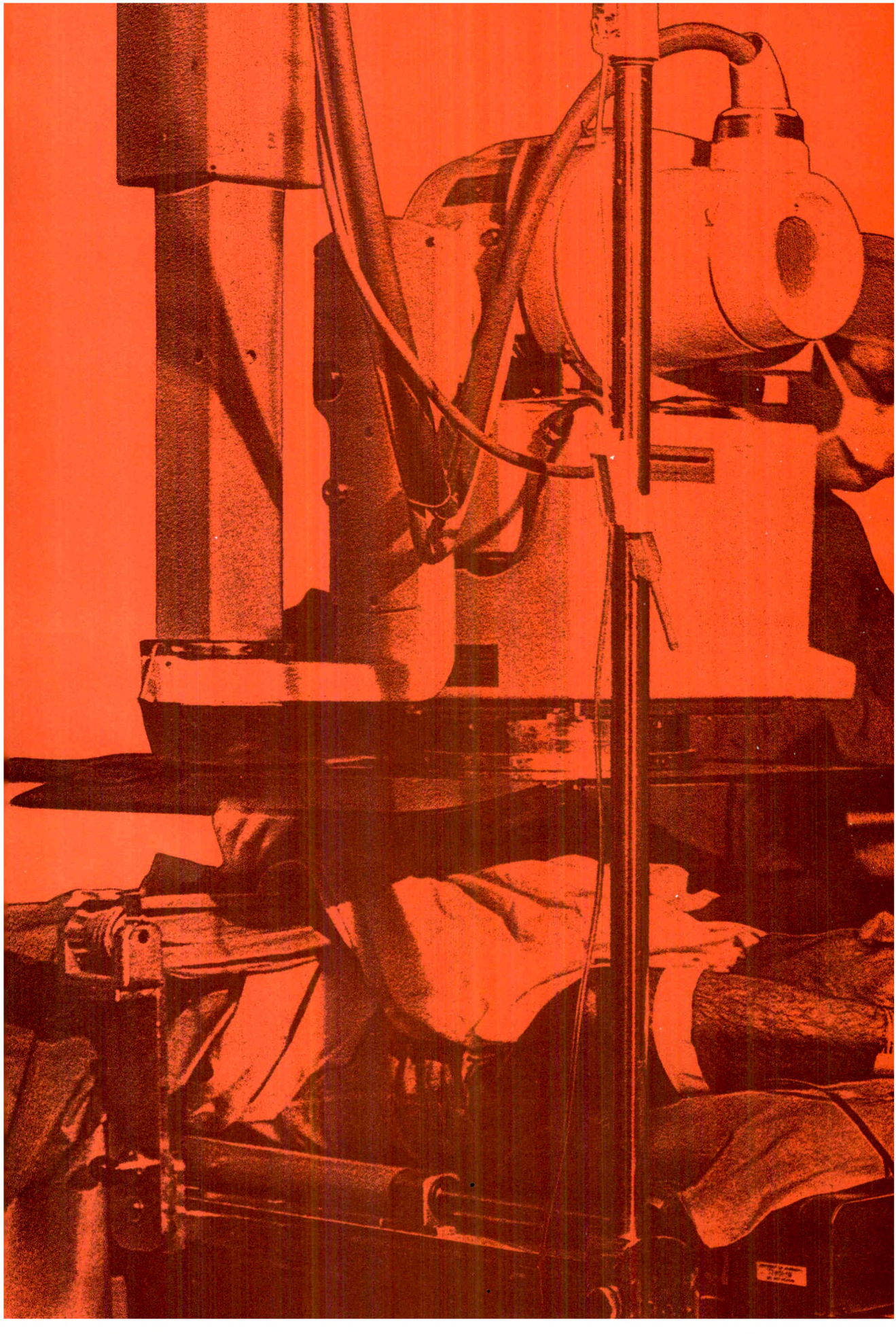

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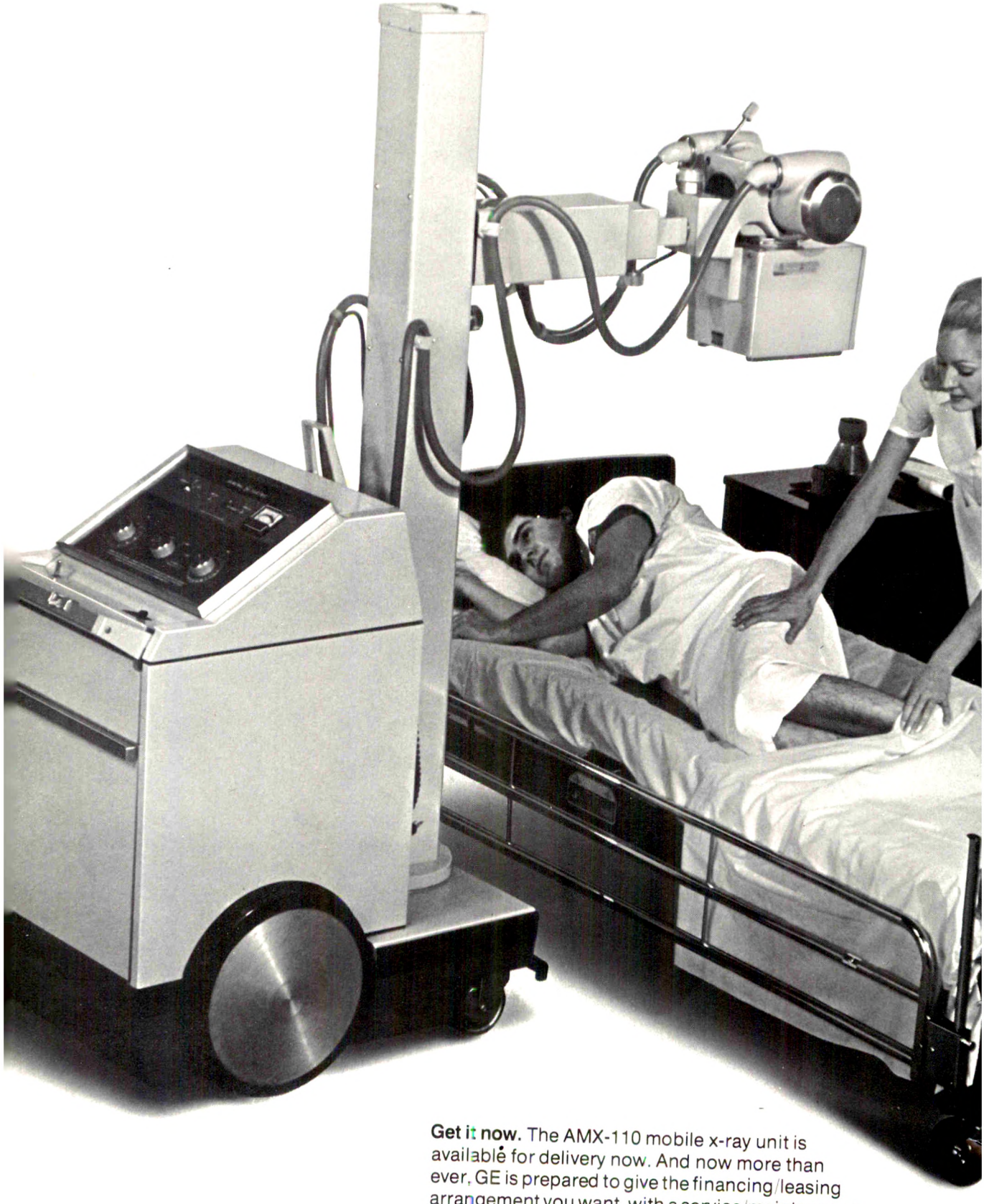

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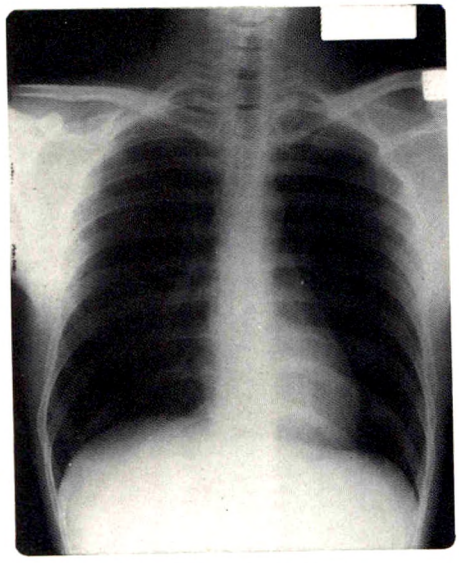

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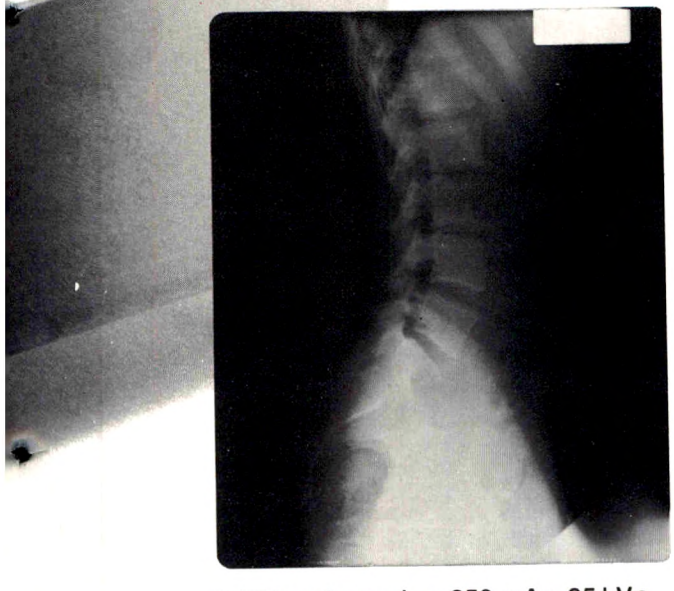

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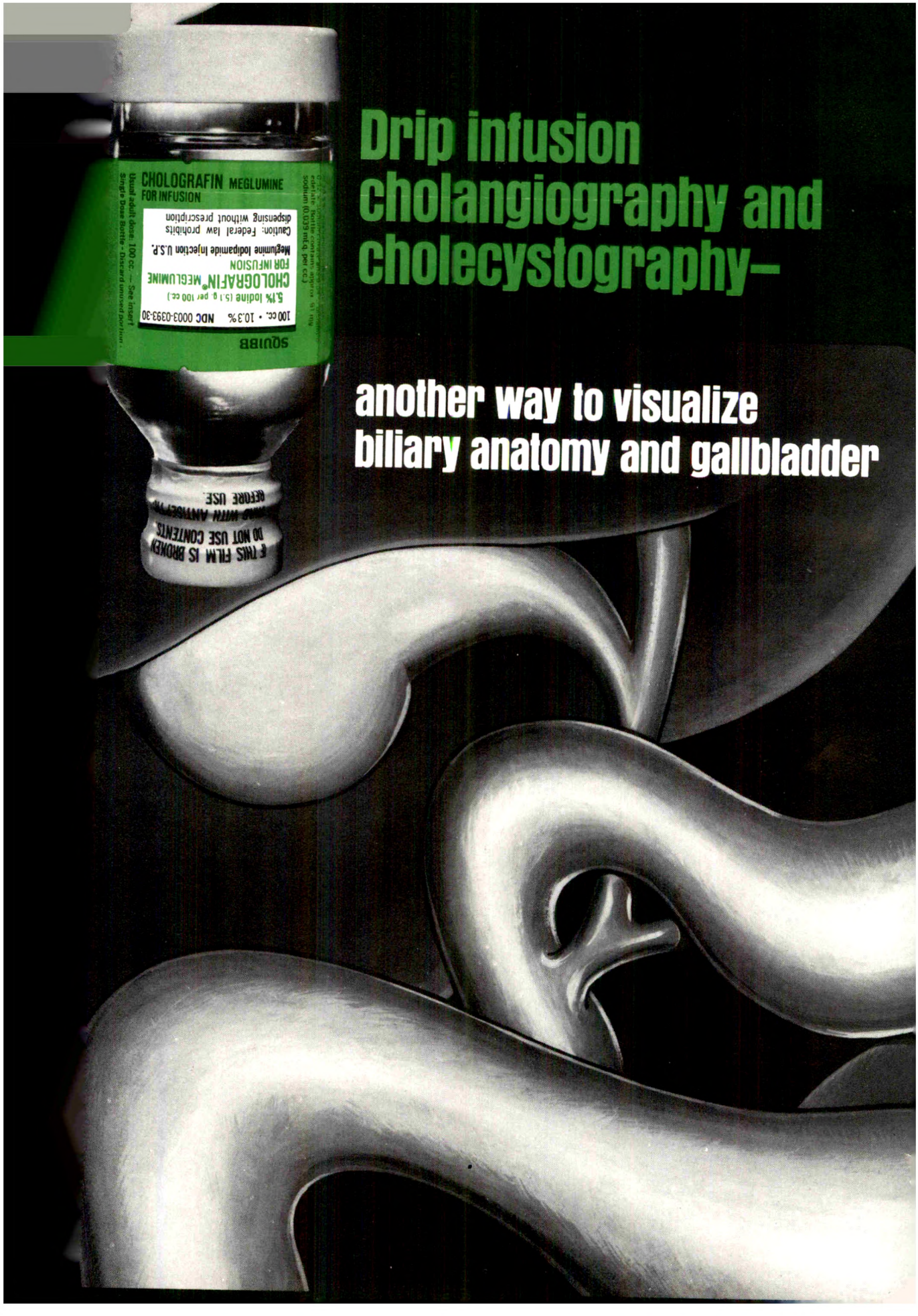
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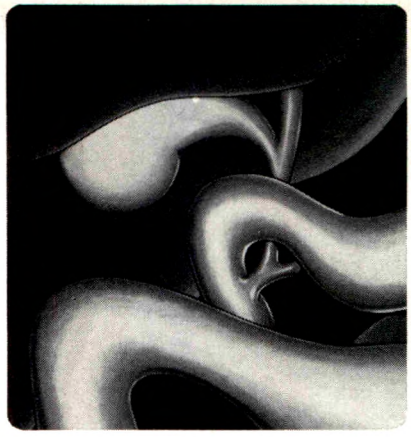

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- **Lower incidence of adverse reactions with drip infusion**
  Drip infusion—7.4% (10 of 135 patients) had reactions
  Injection—19% (12 of 63 patients) had reactions
  See brief summary on next page for reactions which can occur.
- **Good visualization with both techniques**
  Drip infusion—84.4% were of excellent to fair quality
  Injection—75.4% were of excellent to fair quality
- **Methods of administration**
  Drip infusion—100 ml. of 10.3% meglumine iodipamide infused over a 30-minute period
  Injection—20 ml. of 52% meglumine iodipamide injected over a 10-minute period

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ready-to-use for drip infusion cholangiography and cholecystography

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*Information on file at Squibb Institute for Medical Research.

For brief summary, see next page.

for patients undergoing cholangiography and cholecystography

CHOLOGRAFIN® MEGLUMINE FOR INFUSION

(Meglumine Iodipamide Injection U.S.P.)

CHOLOGRAFIN® MEGLUMINE

(Meglumine Iodipamide Injection U.S.P.)

Cholografin Meglumine for Infusion (Meglumine Iodipamide Injection U.S.P.) is a sterile aqueous solution providing 10.3% meglumine iodipamide with 0.32% sodium citrate as a buffer and 0.04% disodium edetate as a sequestering agent. The bound iodine content is about 5.1% (5.1 g./100 ml.). *The solution contains approximately 0.91 mg. (0.039 mEq.) sodium per ml. (91 mg./100 ml.).*

Cholografin Meglumine (Meglumine Iodipamide Injection U.S.P.) is a sterile aqueous solution providing 52% meglumine iodipamide with 0.32% sodium citrate as a buffer and 0.04% disodium edetate as a sequestering agent. The bound iodine content is about 26% (5.2 g./20 ml.). *The solution contains approximately 0.91 mg. (0.039 mEq.) sodium per ml. (18.2 mg./20 ml.).*

CONTRAINDICATIONS: Contraindicated in patients hypersensitive to salts of iodipamide; in patients exhibiting sensitivity reactions to the test dose; in the presence of concomitant severe renal and liver function impairment.

WARNINGS: Intravenous or intra-arterial injections of contrast media have been shown to promote the phenomenon of sickling in persons homozygous for sickle cell disease. Perform thyroid function tests, if indicated, before administration of meglumine iodipamide since iodine-containing contrast media may alter results of such tests. A history of sensitivity to iodine *per se* or to other contrast agents is not an absolute contraindication to the use of meglumine iodipamide but calls for extreme caution in administration.

Usage in Pregnancy: The safety of meglumine iodipamide for use during pregnancy has not been established; therefore, it should be used in pregnant patients only when, in the judgment of the physician, its use is deemed essential to the welfare of the patient.

PRECAUTIONS: Diagnostic procedures involving use of contrast agents should be performed under the direction of personnel with prerequisite training and a thorough knowledge of the particular procedure. Appropriate facilities should be available for coping with situations which may arise as a result of the procedure and for emergency treatment of severe reactions to the contrast agent itself; competent personnel and emergency facilities should be available for at least 30 to 60 minutes after I.V. administration since severe delayed reactions have been known to occur. These severe life-threatening reactions suggest hypersensitivity to the contrast agent. A personal or family history of asthma or allergy or a history of a previous reaction to a contrast agent warrants special attention and may predict more accurately than pretesting the likelihood of a reaction although not the type nor severity of the reaction in the individual. The value of any pretest is questionable. The pretest most performed is the slow I.V. injection of 0.5 to 1.0 ml. of the preparation prior to injection of the full dose; however, the absence of a reaction to the test dose does not preclude the possibility of reaction to the full diagnostic dose. Should the test dose produce an untoward response, the necessity for continuing the examination should be re-evaluated. If deemed essential, examination should proceed with all possible caution. In rare instances, reaction to the test dose may be extremely severe; therefore, close observation and facilities for emergency treatment are indicated. The admixture of Benadryl (Diphenhydramine Hydrochloride) with these meglumine iodipamide preparations may cause a precipitate which may form in the syringe or tubing; if antihistamines are administered concomitantly, they should **not** be mixed with the contrast agent but administered at another site. When the 52% meglumine iodipamide preparation is used, some clinicians feel it may be advisable to have a continuous I.V. infusion running prior to administration of the drug.

ADVERSE REACTIONS: Local reactions at the site of infusion or injection are not observed unless excessive amounts are extravasated during the infusion or injection. After too rapid administration mild transient symptoms such as restlessness, sensations of warmth, sneezing, perspiration, salivation, flushing, pressure in the upper abdomen, dizziness, nausea, vomiting, chills, fever, headache, pallor and tremors may occur. These symptoms disappear when the infusion or injection has been completed. Rarely, swollen eyelids, laryngospasm, respiratory difficulties, hypotension, cardiac reactions and cyanosis have been reported. Hypersensitivity reactions may occur. In rare instances despite the most careful sensitivity testing, anaphylactoid reactions may occur. Renal function tests may be altered and renal failure may occur.

For full information, consult package inserts.

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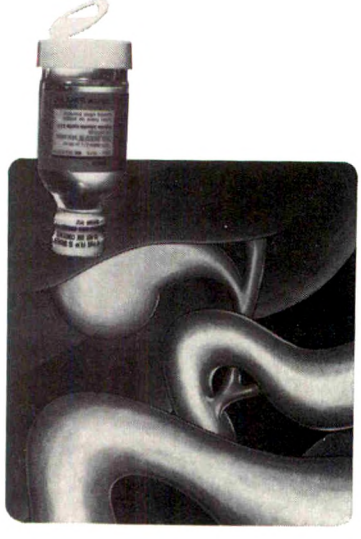

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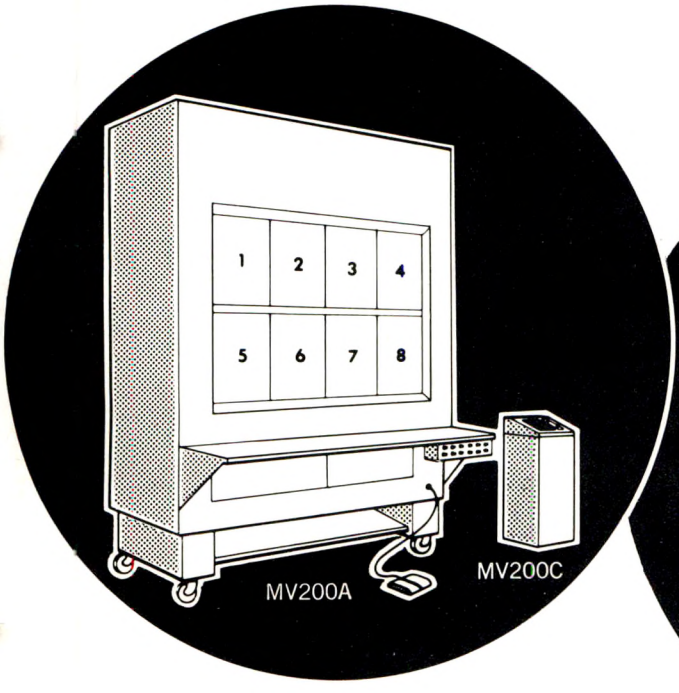

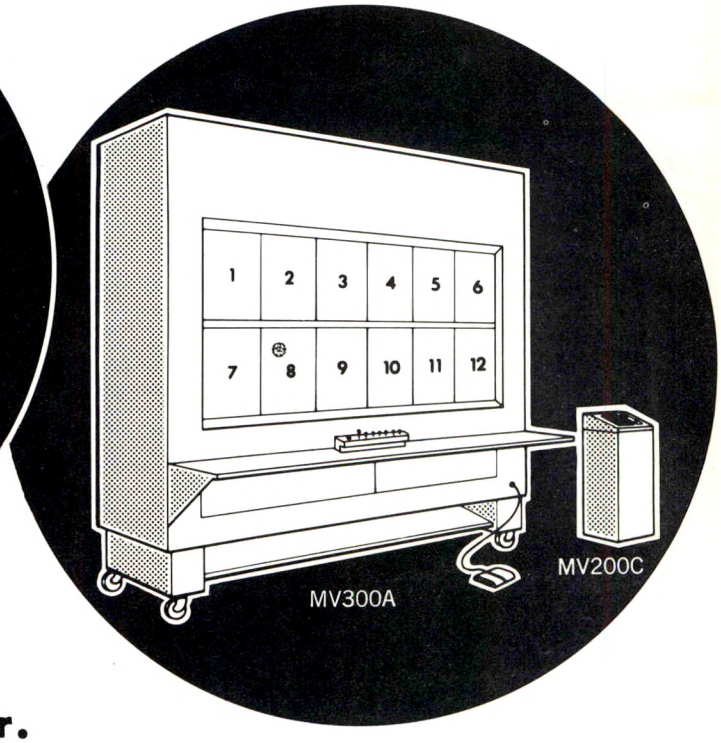

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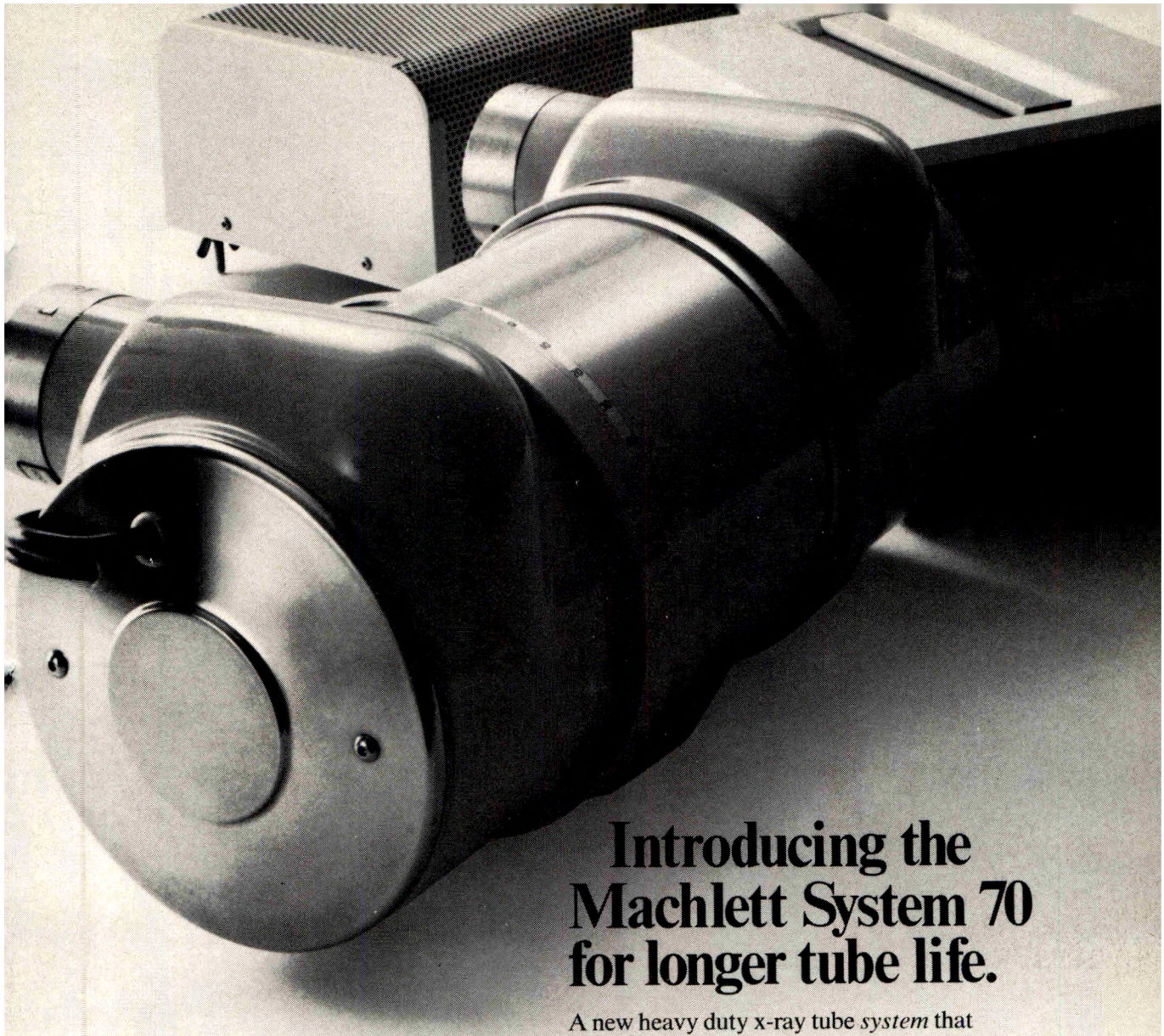

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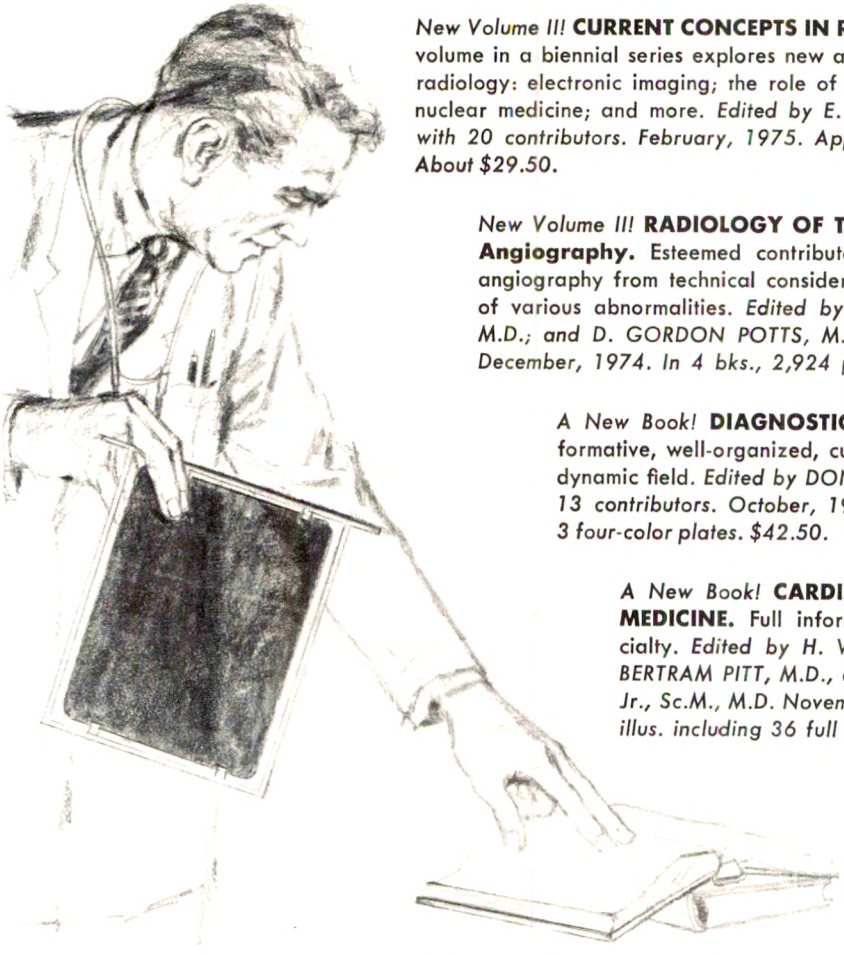

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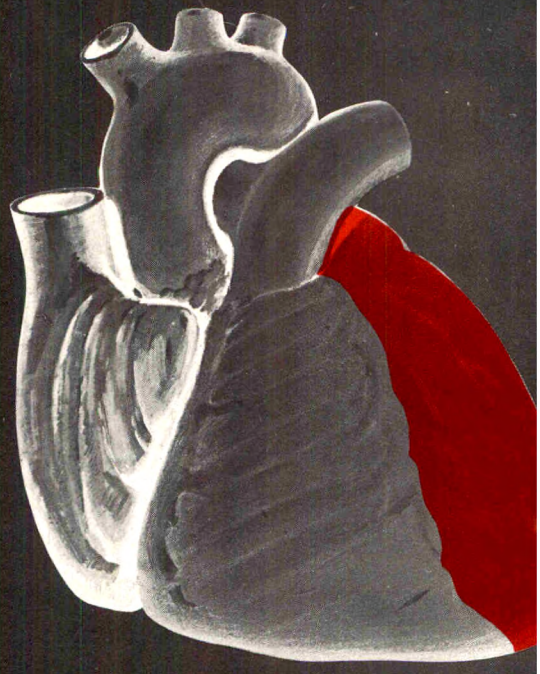

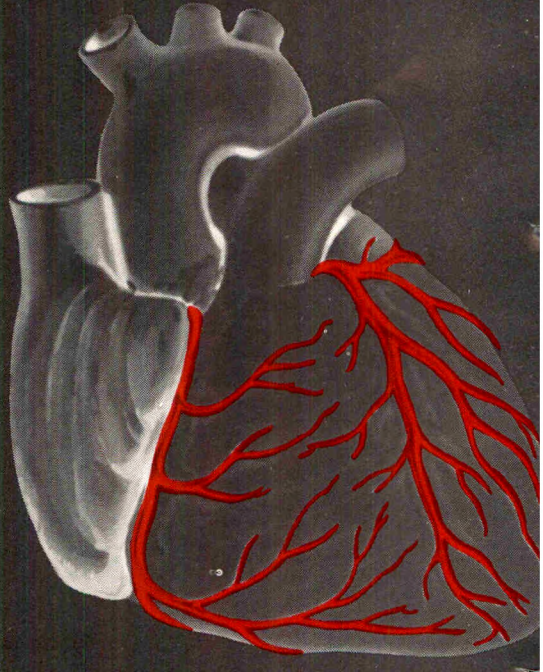

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Contraindications: In patients with a hypersensitivity to salts of diatrizoic acid. Urography contraindicated in patients with anuria.

Warnings: A definite risk exists with the use of contrast agents in excretion urography in patients with multiple myeloma. There has been anuria with progressive uremia, renal failure and death. This risk of the procedure in these patients is not a contraindication; however, partial dehydration in preparation for study is not recommended since it may predispose for precipitation of myeloma protein in renal tubules. No therapy, including dialysis, has been successful in reversing this effect. Myeloma should be considered in persons over 40 before undertaking urographic procedures.

In cases of known or suspected pheochromocytoma, if the physician feels that the possible benefits outweigh the considered risks, diopaque materials should be administered with extreme caution; however, an absolute minimum of material should be injected, the blood pressure should be assessed throughout the procedure, and measures for treating a hypertensive crisis should be available.

Contrast media may promote sickling in homozygous individuals when injected I.V. or intra-arterially. Although a history of sensitivity to iodine *per se* or to other contrast media is not an absolute contraindication, administration of diatrizoate requires extreme caution in such cases. Renografin-76 should be used in pregnant patients only when the physician deems its use essential to the welfare of the patient since safe use during pregnancy has not been established. Perform thyroid function tests prior to administration of Renografin-76 since iodine-containing contrast agents may alter the test results.

Weigh the inherent risks against necessity in performing *angiocardiography* in cyanotic infants and patients with chronic pulmonary emphysema. In *pediatric angiocardiography*, a dose of 10 to 20 cc. may be particularly hazardous in infants weighing less than 7 kg.; this risk is probably significantly increased if these infants have preexisting right heart "strain," right heart failure, and effectively decreased or obliterated pulmonary vascular beds. Perform *urography* with extreme caution in persons with severe concomitant hepatic and renal disease. Perform *selective coronary arteriography* only in selected patients and those in whom expected benefits outweigh the procedural risk.

Precautions: Diagnostic procedures involving use of contrast agents should be performed under the direction of personnel with prerequisite training and a thorough knowledge of the particular procedure. Appropriate facilities should be available for coping with situations which may arise as a result of the procedure and for emergency treatment of severe reactions to the contrast agent itself; competent personnel and emergency facilities should be available for at least 30 to 60 minutes after I.V. administration since delayed reactions have been known to occur. These severe life-threatening reactions suggest hypersensitivity to the contrast agent. A personal or family history of asthma or allergy or a history of a previous reaction to a contrast agent warrants special attention and may predict more accurately than pretesting the likelihood of a reaction although not the type nor severity of the reaction in the individual. The value of any pretest is questionable. The pretest most performed is the slow I.V. injection of 0.5 to 1.0 cc. of the preparation prior to injection of the full dose; however, the absence of a reaction to the test dose does not preclude the possibility of reaction to the full diagnostic dose. Should the test dose produce an untoward response, the necessity for continuing the examination should be re-evaluated. If deemed essential, examination should proceed with all possible caution. In rare instances, reaction to the test dose may be extremely severe; therefore, close observation and facilities for emergency treatment are indicated.

Renal toxicity has been reported in a few patients with liver dysfunction who were given oral cholecystographic agents followed by urographic agents; therefore, if known or suspected hepatic or biliary disorder exists, administration of Renografin-76 should be postponed following the ingestion of cholecystographic agents. Consider the functional ability of the kidneys before injecting Renografin-76. Use cautiously in severely debilitated patients and in those with marked hypertension. Bear in mind the possibility of thrombosis when using percutaneous techniques.

In *excretion urography*, adequate visualization may be difficult or impossible in uremic patients or others with severely impaired renal function (see Contraindications). In *aortography* repeated intra-aortic injections may be hazardous; this also applies to *pediatric angiocardiography* particularly in infants weighing less than 7 kg. (see Warnings). In *peripheral arteriography*, hypotension or moderate decreases in blood pressure seem to occur frequently with intra-arterial (brachial) injections; this is transient and usually requires no treatment. Monitor blood pressure during the immediate 10 minutes after injection. It is recommended that *selective coronary arteriography* not be performed for about 4 weeks after diagnosis of myocardial infarction; mandatory prerequisites to this procedure are experienced personnel, ECG monitoring apparatus, and adequate facilities for immediate resuscitation and cardioversion.

Adverse Reactions: Nausea, vomiting, flushing, or a generalized feeling of warmth are the reactions seen most frequently with intravascular injection. Symptoms which may occur are chills, fever, sweating, headache, dizziness, pallor, weakness, severe retching and choking, wheezing, a rise or fall in blood pressure, facial or conjunctival petechiae, urticaria, pruritus, rash, and other eruptions, edema, cramps, tremors, itching, sneezing, lacrimation, etc. Antihistaminic agents may be of benefit; rarely, such reactions may be severe enough to require discontinuation of dosage. There have been a few reports of a burning or stinging sensation or numbness, of venospasm or venous pain, and of partial collapse of the injected vein. Neutropenia or thrombophlebitis may occur. Severe reactions which may require emergency measures (see Precautions) are a possibility and include cardiovascular reaction characterized by peripheral vasodilatation with hypotension and reflex tachycardia, dyspnea, agitation, confusion, and cyanosis progressing to unconsciousness. An allergic-like reaction ranging from rhinitis or angioneurotic edema to laryngeal or bronchial spasm or anaphylactoid shock may occur. Temporary renal shutdown or other nephropathy may occur.

Adverse reactions as a consequence of *excretion urography* include cardiac arrest, ventricular fibrillation, anaphylaxis with severe asthmatic reaction, and flushing due to generalized vasodilation. Risks of *aortography* procedures include injury to aorta and neighboring organs, pleural puncture, renal damage (including infarction and acute tubular necrosis with oliguria and anuria), accidental selective procedure in presence of preexistent rena ease, retroperitoneal hemorrhage from t lumbar approach, spinal cord injury pathology associated with syndrome of t verse myelitis, generalized petechiae, death following hypotension, arrhythmia, anaphylactoid reactions. In *pediatric a cardiography*, arrhythmia and death have curred. During *peripheral arteriography*, he rhage from puncture site, thrombosis o vessel, and brachial plexus palsy (follo axillary artery injection) have occurred. D *selective coronary arteriography* and *sele coronary arteriography with left ventricu raphy*, transient ECG changes (most patie transient arrhythmias (infrequent); ventri fibrillation (from manipulation of cathete administration of medium); hypotension; c pain; myocardial infarction; transient eleva of creatinine phosphokinase (occurred in a 30% of patients tested); fatalities have l reported; hemorrhage, thrombosis, pse aneurysms at puncture site, dislodgme arteriosclerotic plaques, dissection of coro vessels, and transient sinus arrest have curred due to the procedure.

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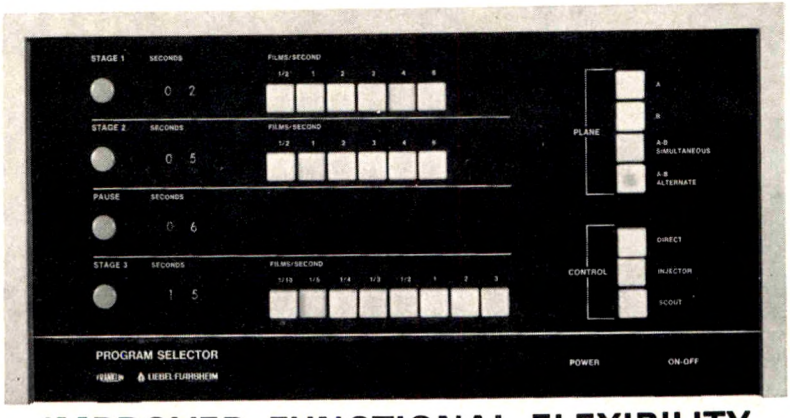

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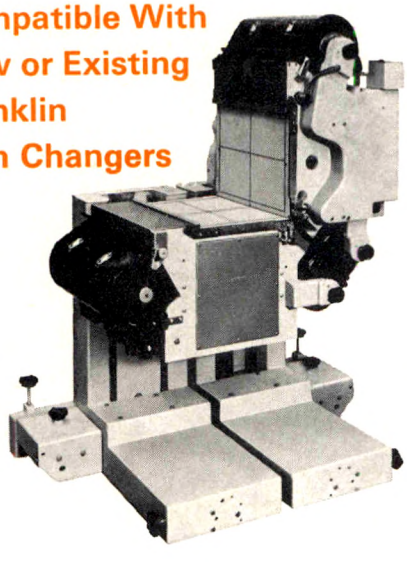

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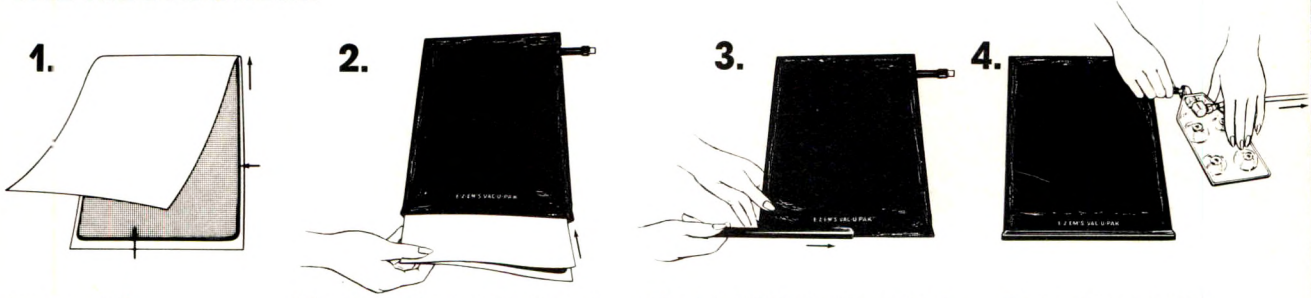

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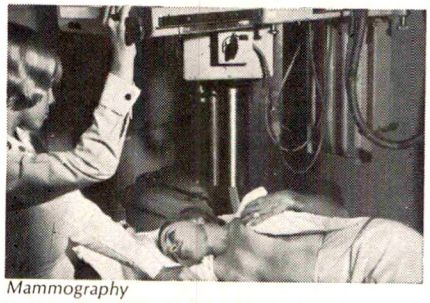

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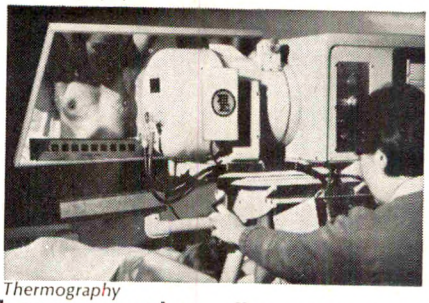

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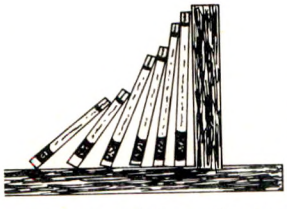

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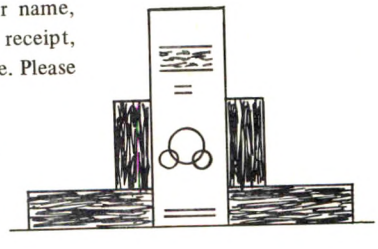

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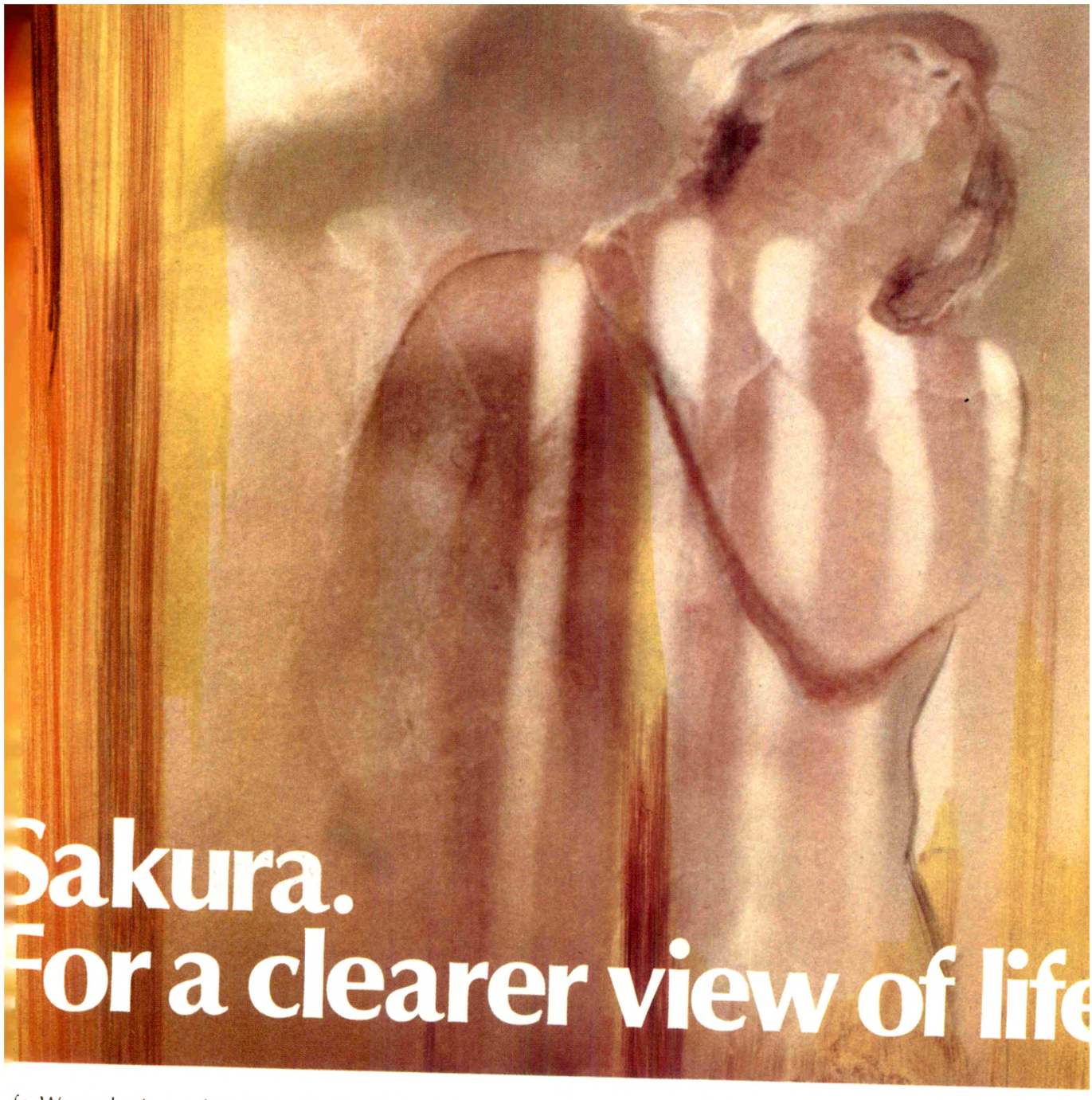

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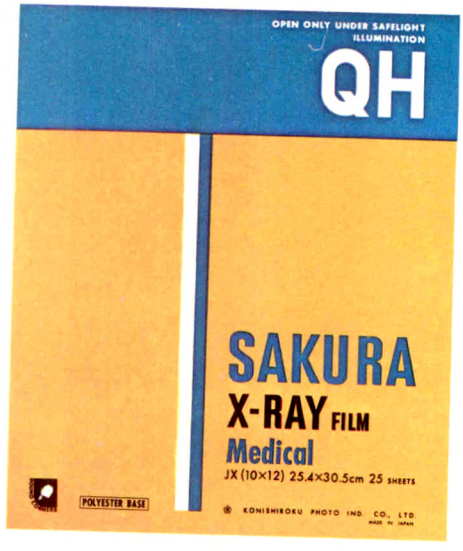

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THE AMERICAN JOURNAL OF ROENTGENOLOGY
RADIUM THERAPY AND NUCLEAR MEDICINE

VOL. 123 FEBRUARY, 1975 NO. 2

THIRD WALTER B. CANNON LECTURE, 1974

THE SURGICAL TREATMENT OF GASTROINTESTINAL ULCER: PAST AND FUTURE*

By J. ENGLEBERT DUNPHY, M.D.†
SAN FRANCISCO, CALIFORNIA

I am very much aware of the honor you bestow upon me as the Third Walter B. Cannon Lecturer and I am doubly grateful in a singularly nostalgic way. I say "doubly grateful," first because my initial introduction to radiology was at the feet of that diagnostic wizard, Merrill Sosman, and ever since the early days at the Brigham, I have viewed the diagnostic radiologist with affection and respect, particularly if he lived up to my Sosmanic standard, which means he must read more out of a film than I have inquired about or even considered!

Secondly, and most importantly, I am grateful and honored because of my personal association with Dr. Cannon and the Cannon family. Bradford Cannon, Dr. Cannon's son, was a classmate in medical school and has been a close friend ever since. Dr. Cannon himself was one of my favorite professors and, in later life, I came to know him through a patient-doctor relationship. Although Walter Cannon was in Russia the year I took physiology, his stature and fame pervaded the medical school. The arguments between Cannon and Britton were legendary and BODILY CHANGES IN PAIN, HUNGER, FEAR, AND RAGE *became a favorite novel. Shock, the role of the sympathetic nervous system and physiologic homeostasis so dominated our thinking and reading that I suspect we rather overlooked the very great importance of his early studies of the gastrointestinal tract. Those of us who were resident surgeons at the Peter Bent Brigham Hospital, however, became keenly aware of this in later years because Dr. Cannon acquired skin cancer as a consequence of his exposure to radiation and over a nu nber of years he was cared for by our Chief, Dr. Elliott Cutler. On frequent occasions, Dr. Cannon would call upon us to dress his wounds or to see a new lesion because he was hesitant to disturb Dr. Cutler. His kindness, thoughtfulness, and modesty distinguished him as much as his scientific contributions. The extraordinary depth and breadth of his contributions to gastroenterology have been well documented recently by Horace Davenport.*[1]

Stories about Dr. Cannon are so numerous that I could make them the subject of this

* From the Department of Surgery, University of California, San Francisco School of Medicine, San Francisco, California.
† Professor and Chairman, Department of Surgery, University of California School of Medicine, San Francisco, California.
[1] DAVENPORT, H. W. "Walter B. Cannon's contribution to gastroenterology." *Gastroenterology*, 1972, *63*, 5.

lecture but I shall limit myself to a favorite few. When he was first appointed to the Chair of Physiology at Harvard, a distinguished Cambridge lady commented to Mrs. Cannon, "Now that your husband is a real professor, I hope he will give up those disgusting researches on the stomach and intestines"!

Dr. Cannon was a consultant to the Peter Bent Brigham Hospital staff and frequently took lunch in the hospital dining room. Over the years it was an historic group, John Homans, David Cheever, Samuel Levine and on occasion Harvey Cushing, Henry Christian, Elliott Cutler and others. On one of these occasions, which Dr. Homans loved to recall, the conversation turned to the cost of living and how quickly one's pocketbook was emptied, no matter how much money with which one started the week. Dr. Cannon said he couldn't quite understand the problem because Mrs. Cannon handled his financial affairs and as his needs were modest, the $1.00 a week which she gave him for spending money was quite sufficient!

One final note: On the occasion of Dr. Cannon's 25th anniversary as Chairman of the Department of Physiology at Harvard, tributes were paid to him by a number of the world's most distinguished scientists. Faculty and students were in attendance with standing room only. His closing remarks after the most fitting tributes had been paid to him were as follows: "As I have listened to what has been said concerning me and my work this afternoon and this evening, I am reminded of a conversation I had years ago with Thomas Salmon, the psychiatrist. Dr. Salmon once had a select acquaintance with some of the important members of the society which dwelt at that time in Sing-Sing Prison. It was characteristic of these prisoners that they were not wholly satisfied with the judgement that was passed upon them. Dr. Salmon told me that not infrequently one of these men would regain a conviction of innocence and a rather satisfactory serenity, indeed at times a comfortable feeling of being a martyr by the simple expedient of persuading himself that he was not the sort of person that people thought he was, in short they had caught the wrong man. I am quite willing to admit that a teacher and worker in science might seem to be properly described by such kind and generous terms as have been used today by my friends but I really believe they caught the wrong man."

It is fitting to close my remarks about Dr. Cannon with this story because I fear that in a very real sense The Society of Gastrointestinal Radiologists has made the same error. In selecting me as the Third Walter B. Cannon Lecturer, you also have caught the wrong man to speak on the past and future of the surgical treatment of gastroduodenal ulceration. There are so many surgeons more capable than I in this field. I think particularly of Lester Dragstedt and Owen Wangensteen who have contributed so much to this field. But then I know radiologists to be practical men and I can hear Alex Margulis say, "Dunphy may not be the very best but he'll be good enough and consider all the travel money we'll save"!

MY own work in gastroduodenal surgery has been almost wholly clinical and rather sharply focused over the years on the management of upper gastrointestinal hemorrhage. Nevertheless, this is an area where the closest cooperation between surgeon and radiologist has been of the utmost benefit to patients. I well recall the early days when many radiologists, including Dr. Sosman, were reluctant to do a GI series on an acutely bleeding patient on the verge of shock and with a stomach full of blood. A major advance in this area came from the Massachusetts General Hospital when Hampton and later Schatski showed that with proper technique and close cooperation, invaluable information could be obtained from barium studies. In the 1940s Stanley Hoerr, Seymour Gray and I were instrumental in persuading Dr. Sosman and his staff that we should adopt this technique at the Brigham. After the publication of our approach to the problem of massive upper GI bleeding, I would frequently be asked when lecturing on the subject what to do when one had a radiologist who insisted that it would be useless for him to attempt a GI series under

those circumstances because he would not be able to see anything. Invariably, my reply was, "Don't insist on him trying because with that attitude to start with he will surely prove his point"! Of course, even today in the presence of a truly exsanguinating hemorrhage there is no recourse but prompt operation. The combination of a cold gastric washout and endoscopy, however, now have made this a field in which contrast studies need not be employed. The big question, of course, is how far will the endoscopists be able to go. With improved equipment, is it possible that contrast studies will rarely be required, a frightening thought for radiologists but I will predict that an adequate examination of the function of the stomach as originally done by Cannon will require the continued use of contrast studies. I must now direct myself to the question of whether surgical operations will be required in the future in the treatment of gastroduodenal ulceration.

As a background, let us look to the turn of the century. The classical study of Cannon and Moser[2] appeared in *The Journal of Physiology* in 1898. Ten years later, in Keen's Surgery,[3] an absolutely classical four-volume compendium of surgery in every detail, there is no mention of contrast studies of the gastrointestinal tract. Radiography is mentioned only as a means of detecting metallic foreign bodies lodged in the esophagus. Indeed, one cannot find the words Roentgen, barium, or x-ray in the very thorough index! "Skiagraphy" in the Diagnosis of Gastric Diseases is mentioned. The contrast medium was capsules of bismuth. The size of the stomach was occasionally outlined by filling the stomach with fluid and introducing a bougie with a small electric lamp near its extremity to transilluminate the gastric wall in the darkroom. Surgery of the stomach and the duodenum was not neglected, however. One hundred forty pages are devoted to the subject and the clear-cut advantages of surgical over medical therapy is thoroughly documented.

The chapter on "Surgery of the Stomach" was contributed by the distinguished Surgeon, A. W. Mayo Robson. Writing on the medical treatment of gastric ulcer, he submits "there were five hundred cases of which no less than forty eight died from peritonitis, thirteen from hematemesis, and twenty eight from other causes. . . . Bad however as this sounds, it is not the worst. These figures do not include any of the cases admitted suffering from what may be called the sequelae and complications of gastric ulcer. They do not take into account the cases admitted for pyloric stenosis (estimated at 10 per cent), hour-glass contraction, gastric dilatation, chronic dyspepsia, constant vomiting, perigastric adhesions, cardiac stenosis, and those numerous other disorders caused by the cicatrization of ulcers healed long since. Nor do they take into account those cases in which carcinoma has developed at the site of the old ulcer. When allowance has been made for all these cases, which certainly cannot be described as cured, it must be admitted that the proportion of patients suffering from gastric ulcer of sufficient severity to require treatment in the hospital, which are discharged as cured in the full sense of the term, in the sense in which a surgeon would use it after an operation, is not nearly so high as is generally imagined. We may thus on ample evidence accept the fact that at least 50 per cent of all cases of ulcer of the stomach treated medically succumb to the disease or to one or other of its complications."

Mayo Robson continues: "How does surgical treatment compare with this? As surgeons, we only see the worst cases that have failed to yield to medical treatment. Yet arguing from my own experience alone, in over 300 operations of various kinds for ulcer of the stomach and its sequelae which failed to yield to medical treatment, the total mortality of all

[2] Cannon, W. B. "Movements of stomach studied by means of roentgen rays." *Am. J. Physiol.*, 1898, *1*, 359.

[3] Keen, W. W. Surgery: Its Principles and Practice. W. B. Saunders Company, Philadelphia, 1914–1921.

operations in this worst class of ulcers, including hourglass contraction and hemorrhage, but excluding perforation, has only been three per cent. But, as shown later, the immediate risk of posterior gastroenterostomy in my private practice in these cases amounted only to 1.7 per cent. And the cases completely relieved of all symptoms were ninety per cent, a proportion that will be still better as experience increases."

As you will recall, gastroenterostomy was the procedure of choice. Mayo Robson continued, "For duodenal ulcer, I do not think any other operative procedure than gastroenterostomy is either necessary or advisable unless there be perforation and even in cases of perforation, if the patient is in a fit condition to bear it, a gastroenterostomy ought to be done at the same time that the perforation is repaired."

Mayo Robson quotes Lord Moynihan's figures "the cases included 171 gastrojejunostomies for chronic ulcer with 2 deaths, 27 cases in which hemorrhage was a prominent symptom with 4 deaths, and 8 cases of hourglass stomach in which gastrojejunostomy had been performed with 3 deaths, thus making 206 cases of ulcer with its complications of hemorrhage and hourglass contraction in which gastrojejunostomy had been performed—a mortality of 4.3 per cent."

The over-all cure rate according to both Moynihan and Mayo Robson for gastroenterostomy was over 90 per cent. With the past as good as that, it is hardly worth talking about the present or the future!

One of the difficulties, of course, is time. The fact is that almost any form of therapy seems to benefit gastroduodenal ulceration. Medication, a change of diet, a change of climate, or a change of doctor all may result in dramatic temporary improvement. Gastric freezing produced dramatic remissions. Recurrences and complications come late. It took 20 years to realize the limitations of posterior gastroenterotomy for duodenal ulcer. The result was an era of gastric resection. The Billroth I operation popularized by Von Haberer in the 1920s was abandoned by him in the 30's because of stomal ulceration. Yet there were many American surgeons still performing Billroth I's with enthusiasm in the 1930s.

The Billroth II had the advantage that it was more difficult to see recurrent stomal ulceration by x-ray but once it was recognized the result was a progressively more radical resection. Eighty per cent subtotal gastrectomy with gastrojejuno-anastomosis produced a low incidence of recurrent ulceration but an extraordinarily high incidence of nutritional complications. Indeed, it provided surgical scholars with the unique opportunity of describing the great variety of postgastrectomy syndromes that developed, the dumping syndrome, bilious vomiting, the afferent loop syndrome, efferent loop obstruction, and recurrent jejunal or gastric ulceration.

It is astonishing how long it took for vagotomy to be thrown into the gastrointestinal sugical equation. The classical studies of Heidenhain and Pavlov on denervated and innervated gastric pouches clearly implicated the role of the vagus in gastric secretion by the turn of this century. Walter Cannon described the effects of vagotomy on gastric motility in 1906.[4]

Latarjet[5] undertook vagotomy in conjunction with posterior gastroenterostomy for gastric lesions including duodenal ulcer in 1922 and partial gastrectomy together with division of the left vagus was reported by Klein in 1929. Klein[6] documented his results with measurements of gastric secretion showing much lower levels in the patients in whom vagotomy had been added. But the real role of vagotomy in gastric surgery was still scarcely visible. Indeed, in the 1930s Dr. Robert Gross of

[4] CANNON, W. G. "Motor activities of stomach and small intestine after splanchnic and vagus section." *Am. J. Physiol.*, 1906, *17*, 429.

[5] LATARJET, M. A. "Resection des nerfs de l'estomac: technique operatoire: resultats cliniques." *Bull. Acad. nat. med.*, 1922, *87*, 681.

[6] KLEIN, E. "Left vagus section and partial gastrectomy for duodenal ulcer with hyperacidity." *Ann. Surg.*, 1929, *90*, 65.

cardiac surgery fame spent a year in Sir David Wilkies laboratory in Edinburgh. Upon his return he called my attention to some sporadic experiments in Wilkies' laboratory on the effect of vagotomy on gastric secretion. He urged both Robert Zollinger and myself to pursue the matter in the laboratory; but both of us were so committed to other projects at the time that nothing was done. A few years later, World War II separated us from all kinds of laboratory research; but, on our return, we found vagotomy for duodenal ulcer an exciting, new, but not yet established procedure. Truncal vagotomy above the diaphragm advocated by Dragstedt[7] and vigorously pursued by Francis Moore[8] left much to be desired. For most of us, a standard two-thirds Billroth II gastric resection remained the procedure of choice.

Being by nature critical and conservative, I was appalled at the proposal of Weinberg[9] and later Farris[10] that pyloroplasty, ligation of the bleeding point, and vagotomy would control massive gastrointestinal hemorrhage. It had to be put to the test, however, and the results were so impressive that James Foster[11] and I became early and enthusiastic advocates of the procedure and remain so today, particularly for the aged or poor-risk patient.

Meanwhile, transabdominal vagotomy combined with either gastroenterostomy or pyloroplasty in the elective treatment of duodenal ulcer gained wide popularity. History must repeat itself, however, and it was not long before the undesirable side effects of vagotomy were realized. Among the first to recognize this and to advocate more limited vagotomy was the late Henry Harkins of the University of Washington. He and his colleague, Griffiths, first urged selective vagotomy and they were among the first to propose super selective, which today is now known as parietal cell or proximal vagotomy.

At this point in time, the parietal cell or proximal vagotomy preserving innervation of the antrum is rapidly becoming the currently "ideal operation." Now 52 years after Latarjet first suggested vagotomy, we find it standing alone as the operation of choice. Professor J. C. Goligher[12] of Leeds writes to me, "We have been using this operation now for just on five years at Leeds and though we have a series of about 300 cases now, the bulk of these have been done for very much lesser periods than that. None the less, the clinical results and the reduction in the incidents of various post gastric operative syndromes are most impressive.[13] I have a very strong hunch that this operation is going to replace truncal and selective vagotomy with drainage and certainly will displace parietal gastrectomy or even antrectomy with vagotomy. We have recently collected information from a number of centers using this operation and it would seem that of some 2,000 cases treated by it, there were only 4 or 5 deaths, which shows that it is a very safe operation indeed."

It is a little too early to say that highly selective vagotomy will replace all other operative procedures in the treatment of duodenal ulcer. It certainly cannot be advocated as yet for gastric ulcer with any degree of enthusiasm. It is fascinating, therefore, to consider that in the interval between when Cannon first reported his studies on the motility of the gastrointestinal tract up to the present time, there is a remarkable similarity in the procedures empirically used in the treatment of gastroduodenal ulceration. Mortality rates and end results have changed remarkably

[7] Dragstedt, L. R., and Owens, F. M., Jr. "Supra-diaphragmatic section of vagus nerves in treatment of duodenal ulcer." *Proc. Soc. Exper. Biol. & Med.*, 1943, *53*, 152.

[8] Moore, F. D., *et al.* "Transdiaphragmatic resection of vagus nerves for peptic ulcer." *New England J. Med.*, 1946, *234*, 241.

[9] Weinberg, J. A. "Vagotomy and pyloroplasty in treatment of duodenal ulcer." *Am. J. Surg.*, 1963, *105*, 347.

[10] Farris, J. M., and Smith, G. K. "Appraisal of long-term results of vagotomy and pyloroplasty in 100 patients with bleeding duodenal ulcer." *Ann. Surg.*, 1967, *166*, 630.

[11] Foster, J. H., *et al.* "Factors influencing mortality following emergency operation for massive upper gastrointestinal hemorrhage." *Surg., Gynec. & Obst.*, 1963, *117*, 257.

[12] Goligher, J. C. Personal comment.

[13] Amdrup, E., *et al.* "Clinical results of parietal cell vagotomy (highly selective vagotomy) two to four years after operation." *Ann. Surg.*, 1974, *180*, 279.

little despite a steady move from empiricism to science. Bayliss and Starling described secretin in 1902.[14] Edkins,[15] a few years later, described a chemical mechanism for gastric secretion and gave the name gastrin to the active principal. In the last decade, a veritable torrent of studies of the interaction of gastrointestinal hormones and gastric secretion has inundated the medical literature. In recent times, it is fair to state that the name of Morton Grossman has been identified with as many of these elucidations as any. I have asked him to comment on the future of surgery for peptic ulcer.[16] He replied as follows, "You ask whether ulcer will be eliminated in the sense that polio has been eliminated. I don't think so. Nothing we now know about ulcer and nothing now going on in ulcer research provides any lead toward wiping out ulcer the way polio was wiped out. It seems unlikely that that can be accomplished until we have better insight into the causes of ulcer. At present we know only about one of the permissive factors, acid and pepsin, and nothing about the primary causes.

You ask whether, if the disease cannot be eliminated, it can at least be controlled by nonsurgical means. I think the prospects for this are excellent. I find no flaw in the premise that if gastric acidity can be reduced enough over enough hours per day and over enough days that ulcers will heal and new ones won't form. We know from experience with operations for ulcer how much reduction of gastric acid is needed to get this result. I see no reason to doubt that pills would be as effective as operations if pills caused as much reduction of acid as operations. We are now beginning to get drugs that give promise of producing the degree of suppression of acid secretion that is required. The best candidates are histamine, H2 receptor blockers and modified prostaglandins. If these drugs prove to be sufficiently nontoxic, they should be effective in causing ulcers to heal. But even if these drugs are as effective as we hope, their role in the long term management of the disease is uncertain. Recurrence and complications are the main things one wants to control. The pills act only so long as they are taken. Will the patient and the doctor prefer lifelong pill-taking to an operation? I don't know the answer. I assume that some will opt for one, some the other.

Finally you ask about the future of operations in vogue today. I find the new operation of proximal gastric vagotomy quite appealing. If the claims are confirmed and if acid reduction is as persistent as with truncal vagotomy, then I should think that it would become the standard operation for duodenal ulcer. Antrectomy could then be reserved for recurrences after this simpler operation."

Dr. Lawrence Way[17] in my own Department emphasizes our lack of understanding of the epidemiology of ulcer. "A relatively unpublicized observation is the great fluctuation in incidence of duodenal ulcer over the years. At present there is a marked decline despite the feeling that society is increasingly 'stressful'. The greatest incidence of duodenal ulcer occurred in persons born in the decade beginning 1890 and it has dropped steadily since then. Moreover the available statistics suggest the disease was much less common earlier in the nineteenth century. These observations hold true for overall incidence as well as for complications. For example, several excellent studies agree that throughout developed societies the prevalence of perforation is now only one half of what it was just twenty years ago. In the absence of a good explanation of this phenomenon, it is obvious that there is much to learn about etiology and it is hazardous to predict how extensively the population will be affected in the future."

[14] BAYLISS, W. M., and STARLING, E. H. "Mechanism of pancreatic secretion." *J. Physiol.*, 1902, *28*, 325.

[15] EDKINS, J. S. "On chemical mechanism of gastric secretion." *Proc. Roy. Soc., London. ser. B.*, 1905, *76*, 376.

[16] GROSSMAN, M. Personal comment.

[17] WAY, L. Personal comment.

In addition to Drs. Grossman and Way I have asked several distinguished surgeons for their views on the future of surgery for peptic ulcer. There was a remarkable unanimity of opinion, including the conviction that the development of H_2 blocking agents will prove to be a major breakthrough in the control of gastric acidity. How effective this will be in the long range control of ulceration is, of course, still problematical. Patients may not take their medication. There may be a variety of complications from the therapy. In general, however, there was a strong feeling that the non-surgical management of ulcer would be substantially improved in the future but that the disease was not likely to disappear and that so long as it was with us, there would be the intractable cases and the complications.

In short, all of my consultants were in agreement that the problem of gastroduodenal ulceration will not be solved, that the incidence is unpredictable, that medical therapy will be substantially better but that surgical therapy will continue to be required. Without exception, all lean strongly towards the adoption of the new operation of parietal cell vagotomy. If for no other reason, its low mortality will make it the first truely substantial surgical advance since the reports of Mayo Robson and Moynihan in Keen's Surgery in 1908.

There is the story as well as I can summarize it. As for the gastrointestinal radiologist I would anticipate that so long as the disease exists his acumen and skills will be in demand. Let me conclude by saying that at this point in time, I think Walter B. Cannon would be astonished at how much he knew about gastric physiology and how closely his studies presaged the diagnostic and therapeutic advances of the next century.

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ROENTGEN PROBLEMS IN EVALUATING THE ATROPHIC STOMACH OF THE ELDERLY

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IT has been shown at autopsy and on endoscopic biopsy specimens that gastric atrophy increases in incidence in the older age groups. In one study, 50 per cent of asymptomatic patients over 60 years of age showed atrophic changes in the gastric mucosa. These changes were usually associated with achlorhydria, which also increases in incidence with age.[18]

The usual roentgen findings noted in gastric atrophy and atrophic gastritis have been well described and correlated with the gastric acid output.[2,3,9,11,15] It has not been emphasized, however, that some elderly patients show other roentgen findings which may cause serious difficulty in differential diagnosis.

This is a study of 17 such collected cases in which the following diagnostic difficulties were encountered: (1) simulation of scirrhous carcinoma of the distal stomach—8 cases; (2) gastric retention of food after an overnight fast—6 cases; and (3) gastric retention of oral cholecystographic medium 14 hours after ingestion—3 cases.

ROENTGEN FINDINGS

(1) *Simulation of scirrhous carcinoma of the distal stomach*—8 cases. Seven of the patients were female and 1 male with their ages varying from 65 to 77 years. The roentgenograms of the stomach in all these cases showed the tubular stomach, and the speckled and bald fundus characteristic of gastric atrophy. In addition, however, the distal stomach was more limited in distensibility with straightening of the lesser curvature and indentations of the greater curvature, producing a pseudosacculated appearance (Fig. 1*A*; and 2*A*). The peri-

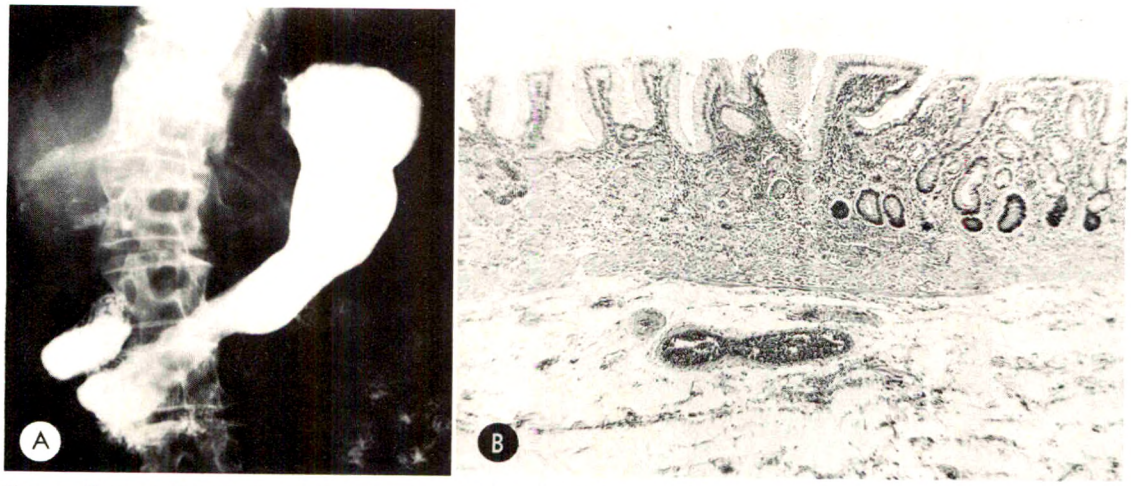

FIG. 1. Case 11. *Gastric atrophy*. A 77 year old female with weight loss.
(*A*) Tubular stomach with limited distensibility of the antrum and flattening of the lesser curvature. Peristaltic activity was absent. At surgical exploration no neoplasm was found. (*B*) Postmortem histologic section of the stomach showing mucosal atrophy with areas of intestinalization and lymphocytic and plasma cell infiltration. (H & E stain ×125.)

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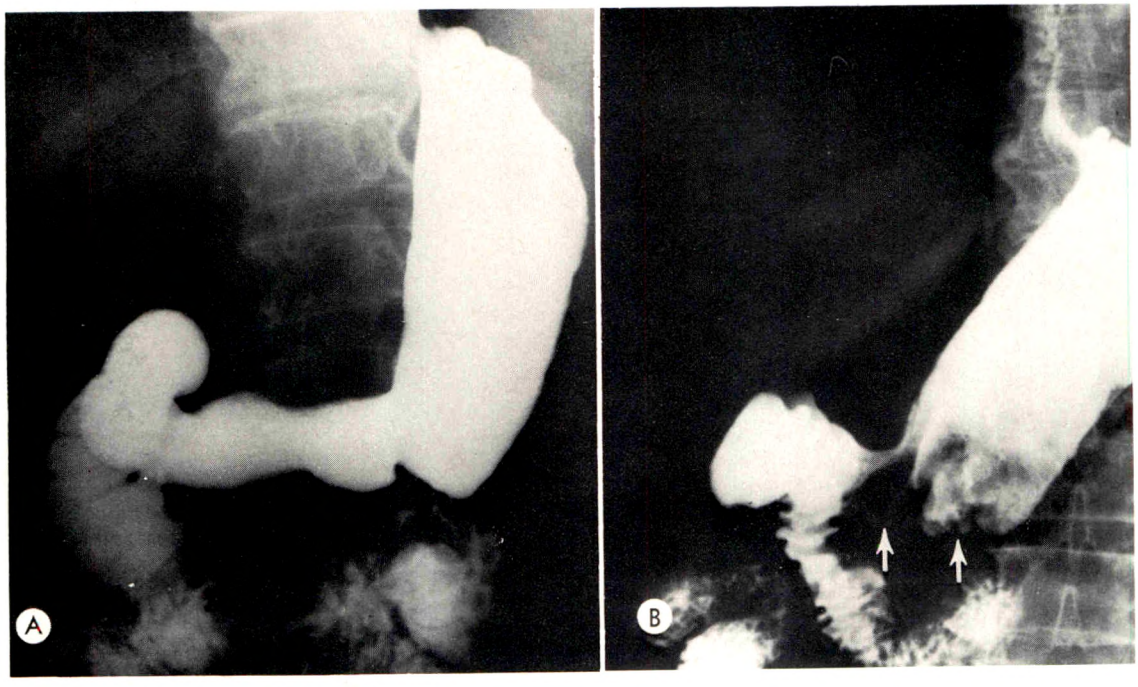

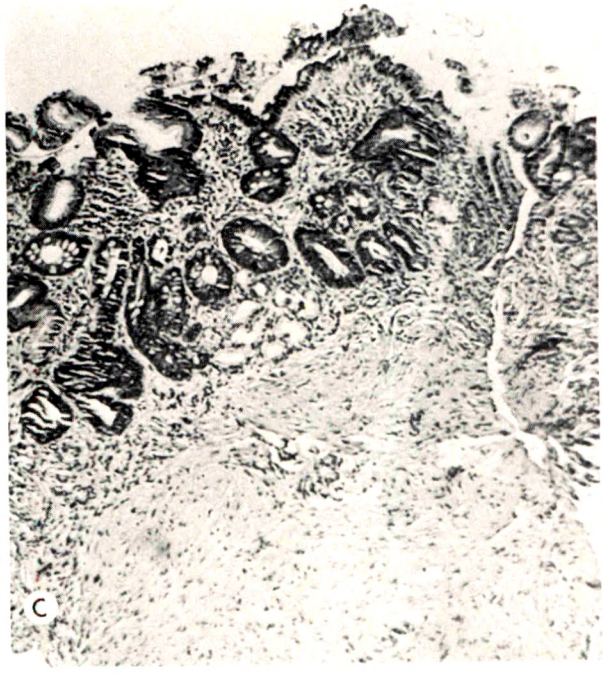

Fig. 2. Case III. *Gastric atrophy*. A 67 year old female with epigastric distress.

(*A*) Prone frontal roentgenogram. Note the limited distensibility of the stomach, the flattening of the lesser curvature and the indentations of the greater curvature. (*B*) Supine frontal roentgenogram. Note the scalloped irregularity of the greater curvature (arrows). Gastroscopy showed changes consistent with mucosal atrophy. (*C*) Gastroscopic biopsy specimen of the greater curvature of the body of the stomach showing marked mucosal atrophy. (H&E stain ×125.)

stalsis was absent or minimal. Two cases also showed a scalloped coarse irregularity of the distal greater curvature (Fig. 2*B*). Cases I and II were explored because of the diagnosis of scirrhous carcinoma. The surgical findings were those of normally pliable stomachs, which on biopsy showed gastric atrophy. Case II expired postoperatively. Postmortem study of the stomach showed a thin mucosa with absence of normal folds. Microscopically, there was marked diffuse mucosal atrophy with areas of intestinalization (Fig. 1*B*). In Case III, gastroscopic biopsy was performed

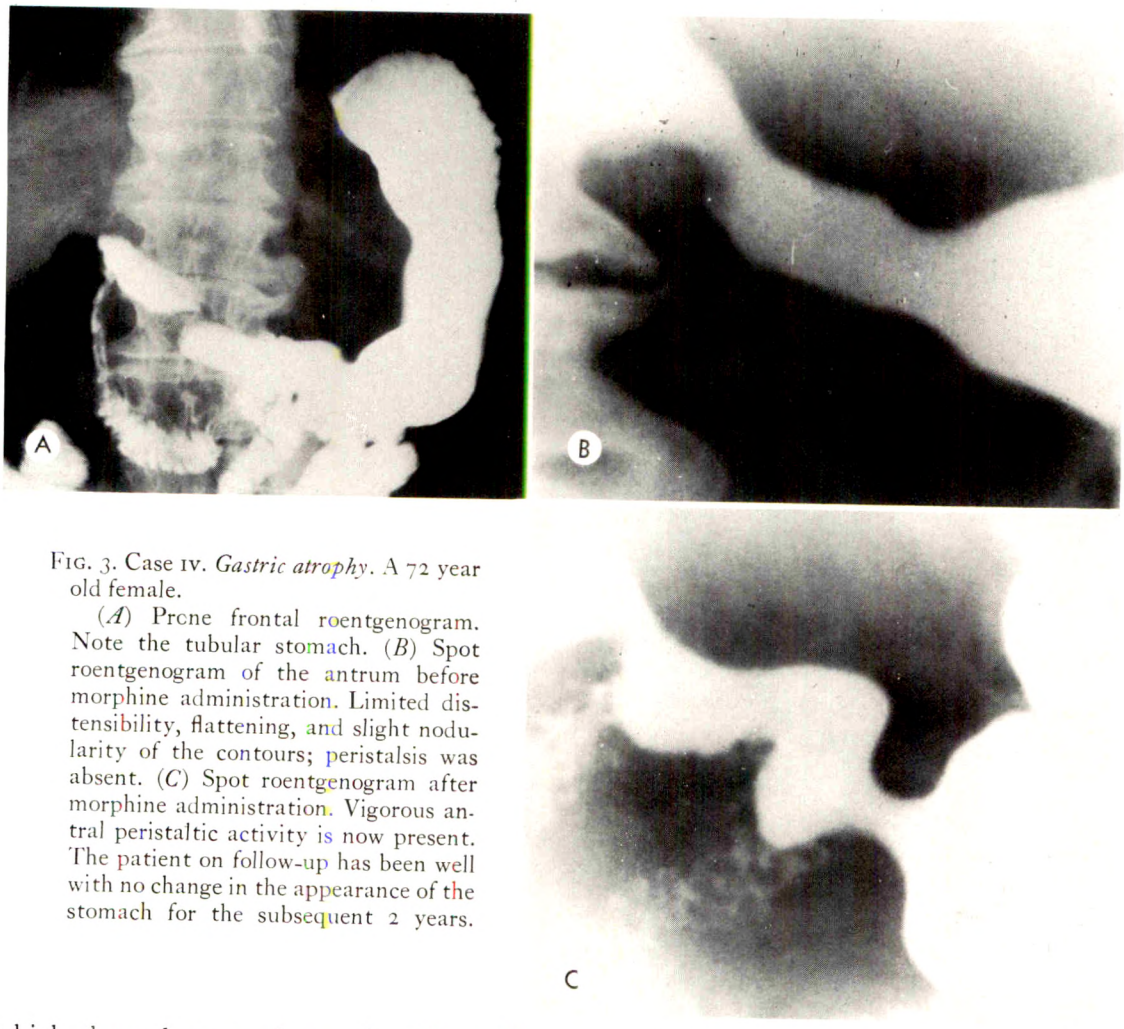

FIG. 3. Case IV. *Gastric atrophy*. A 72 year old female.

(*A*) Prone frontal roentgenogram. Note the tubular stomach. (*B*) Spot roentgenogram of the antrum before morphine administration. Limited distensibility, flattening, and slight nodularity of the contours; peristalsis was absent. (*C*) Spot roentgenogram after morphine administration. Vigorous antral peristaltic activity is now present. The patient on follow-up has been well with no change in the appearance of the stomach for the subsequent 2 years.

which showed mucosal atrophy (Fig. 2*C*). The patient subsequently died of unrelated causes and at postmortem examination the findings were confirmed. Case IV had a barium study of the stomach after morphine administration which stimulated prominent peristalsis of the distal stomach (Fig. 3, *A–C*). No further work-up was done on the other 4 cases, but the clinical course and follow-up indicated the absence of malignancy.

(2) *Gastric retention of food after an overnight fast.* Gastric retention of food after an overnight fast is usually due to gastric outlet obstruction.[8] In these 6 cases, however, the barium study showed normal peristalsis with no delay of pyloric opening or gastric emptying. In addition, the stomach showed the usual roentgen features of gastric atrophy but without changes simulating scirrhous carcinoma. The patients were 3 females and 3 males and varied in age from 68 to 75 years. In 4 cases food retention was intermittent, with demonstration on 1 or 2 studies and not on others (Fig. 4, *A–C*). Questioning of the patients and the nursing personnel indicated that the patients had not ingested any food within the time of the prescribed overnight fast.

(3) *Gastric retention of oral cholecystographic medium 14 hours after ingestion.* Gastric retention of oral cholecystographic contrast medium usually indicates gastric outlet obstruction or abnormality in gastric emptying.[7] In the 3 cases reported, there

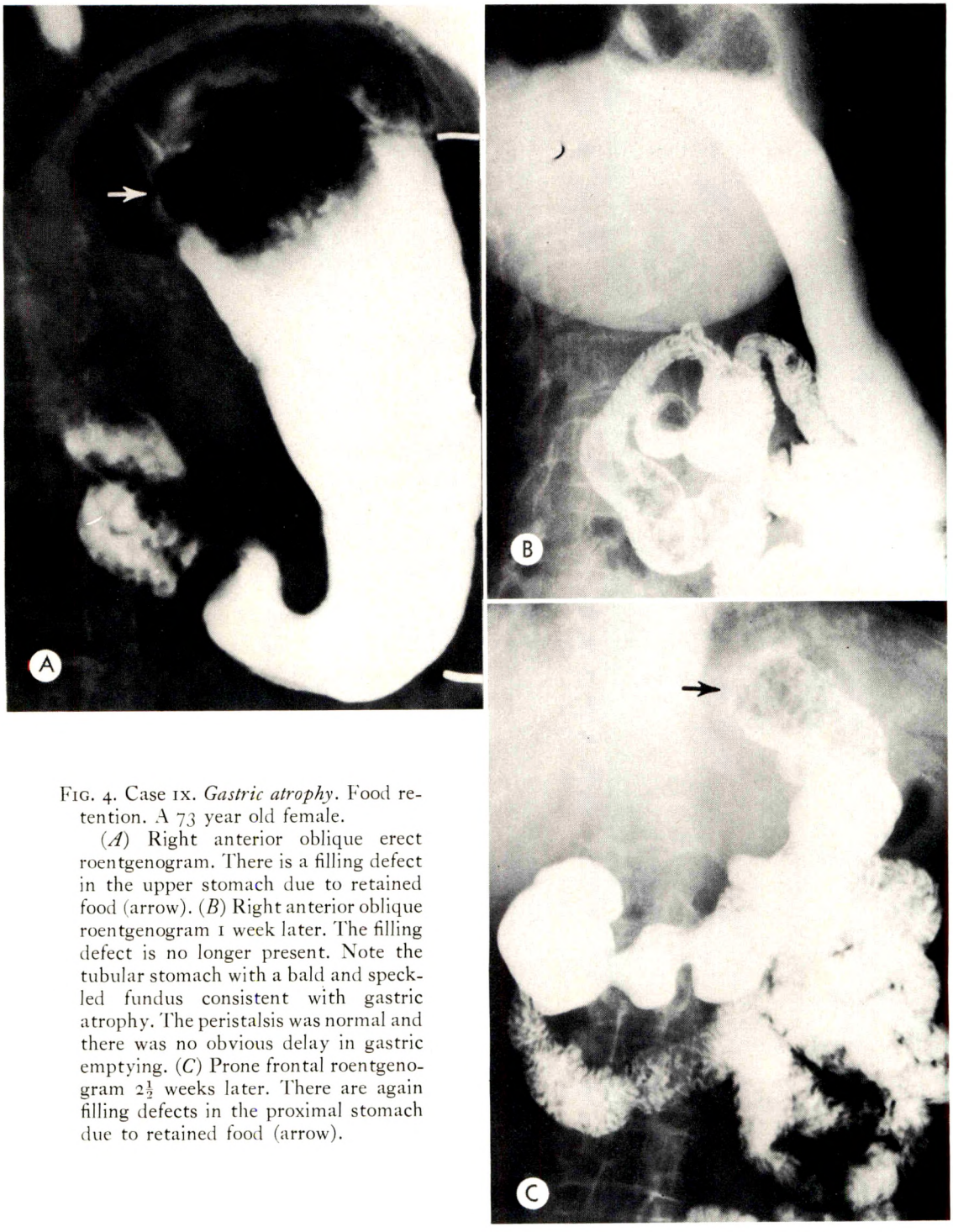

Fig. 4. Case IX. *Gastric atrophy*. Food retention. A 73 year old female.

(*A*) Right anterior oblique erect roentgenogram. There is a filling defect in the upper stomach due to retained food (arrow). (*B*) Right anterior oblique roentgenogram 1 week later. The filling defect is no longer present. Note the tubular stomach with a bald and speckled fundus consistent with gastric atrophy. The peristalsis was normal and there was no obvious delay in gastric emptying. (*C*) Prone frontal roentgenogram 2½ weeks later. There are again filling defects in the proximal stomach due to retained food (arrow).

was a significant amount of contrast substance retained in the stomach. In 2 cases the gallbladder showed faint visualization and in the 3rd nonvisualization. The subsequent barium gastric study showed the roentgen features of gastric atrophy similar to the cases in Group 2, but with no obvious delay in pyloric opening or gastric

emptying. The patients were 2 females and 1 male and varied in age from 69 to 89 years.

DISCUSSION

The narrowing and reduced distensibility of the distal stomach in gastric atrophy, the so-called senile antrum,[6,16] may be due to muscle spasm. Muscular hypertrophy has been noted pathologically in cases of pernicious anemia by Mitchell and Walker.[10] These authors found 4 cases of narrowing of the gastric antrum with scalloping of the contour of the greater curvature presumably due to spasm of the hypertrophied musculature. These changes disappeared following therapy with vitamin B_{12}. Two cases in the current study showed a similar scalloping but did not have pernicious anemia. Presumably the mechanism was the same, that is spasm of the muscularis mucosae. The limited distensibility and abnormal configuration of the distal stomach is probably related to spasm of the muscularis. Silbiger and Donner[16] mention the utility of a morphine study in evaluating such cases. This was used in one of our cases and showed a remarkable stimulation of peristaltic activity.

The mechanism of prolonged gastric retention of food and oral cholecystographic medium in some cases of gastric atrophy is unclear, since barium studies showed no abnormalities in peristalsis, pyloric opening or gastric emptying. The neurogenic gastric hypotonia and reduced motility seen in gastroparesis diabeticorum was not present.[5,13]

The following possible mechanisms may be involved:

(1) Incompetence of the pyloric sphincter with reflux from the duodenum back into the stomach. There is evidence that some patients with pernicious anemia and achlorhydria have an incompetence of the pyloric sphincter allowing bile to reflux back into the stomach.[12]

(2) The gastric emptying of barium may not actually reflect the gastric emptying of food which undergoes digestive changes in the stomach. This process is affected by the absence of acid and the deficiency of peptic enzymes in these patients.[1,14] The type of food ingested the previous evening may thus be a factor and thus explain the fact that such retention is not seen in every study in the same patient. Poor mastication of this ingested food may be an additional factor. The abnormalities of gastric digestion may explain the dyspeptic symptoms seen in many of these patients.[18]

Since studies of the physiology of iopanoic acid have indicated that it dissolves more slowly in acid than in alkaline solution,[4,17] the retention of iopanoic acid in the stomach cannot be attributed to the achlorhydria and higher gastric pH. The possibilities of reflux back into the stomach and abnormality of gastric emptying must be postulated as factors in the observed gastric retention.

These gastric retention phenomena have not been previously reported in patients with senile gastric atrophy. The recognition by the physician that food may be retained in such patients after an overnight fast may prevent the unjustified assumption of a violation of the regimen prescribed for the upper gastrointestinal study. There is no roentgen diagnostic problem in determining that the filling defects are retained food, since this is a simple roentgen finding. Retention of oral cholecystographic medium may partially explain the deficiencies of gallbladder visualization noted in these cases.

SUMMARY

Gastric atrophy in the elderly may cause problems in the interpretation of gastrointestinal studies.

Seventeen such cases are reported: 8 patients showed limited distensibility and irregularity of the distal stomach simulating scirrhous carcinoma; 6 patients showed gastric retention of food; and 3 patients showed gastric retention of oral cholecystographic medium.

Awareness of these phenomena may prevent serious errors in roentgen diagnosis.

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CROHN'S DISEASE OF THE STOMACH: THE "RAM'S HORN" SIGN*

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ALTHOUGH the terminal small bowel is the most common site to be involved in Crohn's disease, any portion of the gastrointestinal tract may be affected.[2,15,20] Occasionally, even oral and esophageal lesions have been described.[6,12] Gastric and duodenal disease remain uncommon, the incidence of involvement ranging from 0.5 to 4.0 per cent.[10,23]

In 1950 Comfort *et al.*[3] described 5 patients with granulomatous disease of the duodenum and small bowel, 2 of whom had stomach involvement as well. Three years later, Martin and Carr[19] reported on 2 patients with gastric Crohn's disease. Reviewing the literature in 1964 Pryse-Davies[21] found that 31 patients with gastroduodenal Crohn's disease had been recorded. The author added a further case report of his own.

Although more than 80 reports of gastroduodenal Crohn's disease exist in the literature, histologic proof has been documented in only 22 patients.[1,5,7,23] This is not surprising, as surgery is usually not indicated in the absence of complications such as pyloric obstruction. Many patients were operated on because the roentgenologic appearances of the stomach suggested either carcinoma or chronic peptic ulceration.

In reviewing the roentgen appearance of the stomach, both in our series and those reported in the literature, we have been impressed by the frequency with which the antrum is involved, leading to deformity, tubular narrowing, limited distensibility and poor peristalsis.[1,13,16] These factors combine to give the stomach an unusual shape resembling a sacramental "ram's horn" (Fig. 1).

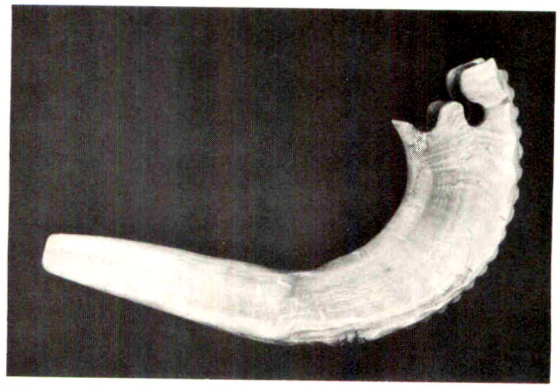

FIG. 1. Ram's horn or sacramental "shofar" used to sound the advent of the Jewish New Year.

We have found this appearance to be most useful in the evaluation of antral narrowing in patients with Crohn's disease; and even in the absence of known Crohn's disease, the presence of this deformity, especially in the younger patient, necessitates full roentgenologic investigation of both large and small bowel in an attempt to document Crohn's disease in these areas and so confirm the diagnosis.

MATERIAL AND METHOD

The patients, 12 in number, ranged in age from 11 to 62 years and averaged 30 years. Nine were male and 3 were female. Ten patients were white, of whom 6 were Jewish. Two were Black. All patients in this study had antral abnormality as well as known Crohn's disease elsewhere in the gastrointestinal tract.

Every patient had small bowel disease of

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varying extent and severity. Duodenal involvement was present in 5 patients, 1 of whom also had esophageal involvement. Four patients had Crohn's disease of the colon (Table 1).

One patient with longstanding Crohn's disease of the stomach, small intestine and colon developed secondary amyloidosis. Steroid therapy was responsible for the development of a gastric ulcer in 1 patient. This healed later when the steroids were withdrawn and medical treatment was instituted for management of the ulcer.

Two patients had both partial gastrectomies and segmental bowel resections.

Four patients underwent gastroscopy and duodenoscopy. Mucosal biopsies were not diagnostic and indicated only subacute inflammatory changes.

REPORT OF CASES

Case 1. G.E., a 21 year old male, became ill in June 1969 with severe abdominal pain, recurring diarrhea and weight loss. A barium meal and follow-through examination showed the presence of Crohn's disease involving the terminal ileum and cecum. In addition, the pyloric antrum was deformed. Its distensibility was limited and a nodular, "cobblestone" mucosal pattern was evident (Fig. 2, *A–D*).

Despite steroid therapy and repeated hospital admissions, the patient's general condition deteriorated and by December he had lost 40 pounds in weight. The patient was admitted to hospital for a right hemicolectomy. An upper gastrointestinal series was again performed prior to surgery, and revealed the development of a benign peptic ulcer on the lesser curve of the stomach at the incisura. The stomach also contained excess fasting secretions. A right hemicolectomy was performed and the patient was discharged from hospital 16 days later. He was placed on a strict regimen and steroid therapy was withdrawn.

In January 1970, the gastric ulcer was re-evaluated roentgenologically and, although still visible, was much smaller. Consequent roentgen examination of the stomach showed roentgenologic disappearance of the peptic ulcer but persistence of the antral deformity. There was, in addition, dilatation of the duodenum by a band-like constriction in its third part. The patient continued to experience abdominal pain with vomiting, although his diarrhea had ceased.

On re-admission to hospital on March 3, 1970, gastroscopy and duodenoscopy were performed. These studies confirmed the presence of coarsened antral mucosa and numerous superficial ulcerations. A gastric mucosal biopsy revealed subacute inflammatory changes.

At laparotomy, no evidence of recurrent disease was evident in the small bowel or proximal colon and the anastomotic site appeared healthy. Obvious Crohn's disease was present involving the stomach. A Billroth II gastrec-

Table I

CASE MATERIAL

Patient	Sex	Age	Race	Endoscopy	Other Sites of Crohn's Disease
D.P.	M	11	B		D., S.I.
G.E.	M	21	W	X	S.I., C.
M.R.	M	62	W (J)	X	S.I., D.
M.M.	M	15	W		S.I.
M.W.	F	23	B	X	S.I., C.
D.S.	M	20	W		E., D., S.I.
R.G.	M	19	W (J)		S.I.
M.B.	F	55	W (J)	X	S.I.
J.T.	M	40	W (I)		D., S.I., C.
J.B.	M	50	W (J)		S.I.
B.B.	M	12	W (J)		S.I.
M.R.	F	24	W (J)		S.I., C., D.

M—Male; F—Female; B—Black; W—White; J—Jewish; I—Italian; D—Duodenum; S.I.—Small Intestine; C—Colon; E—Esophagus

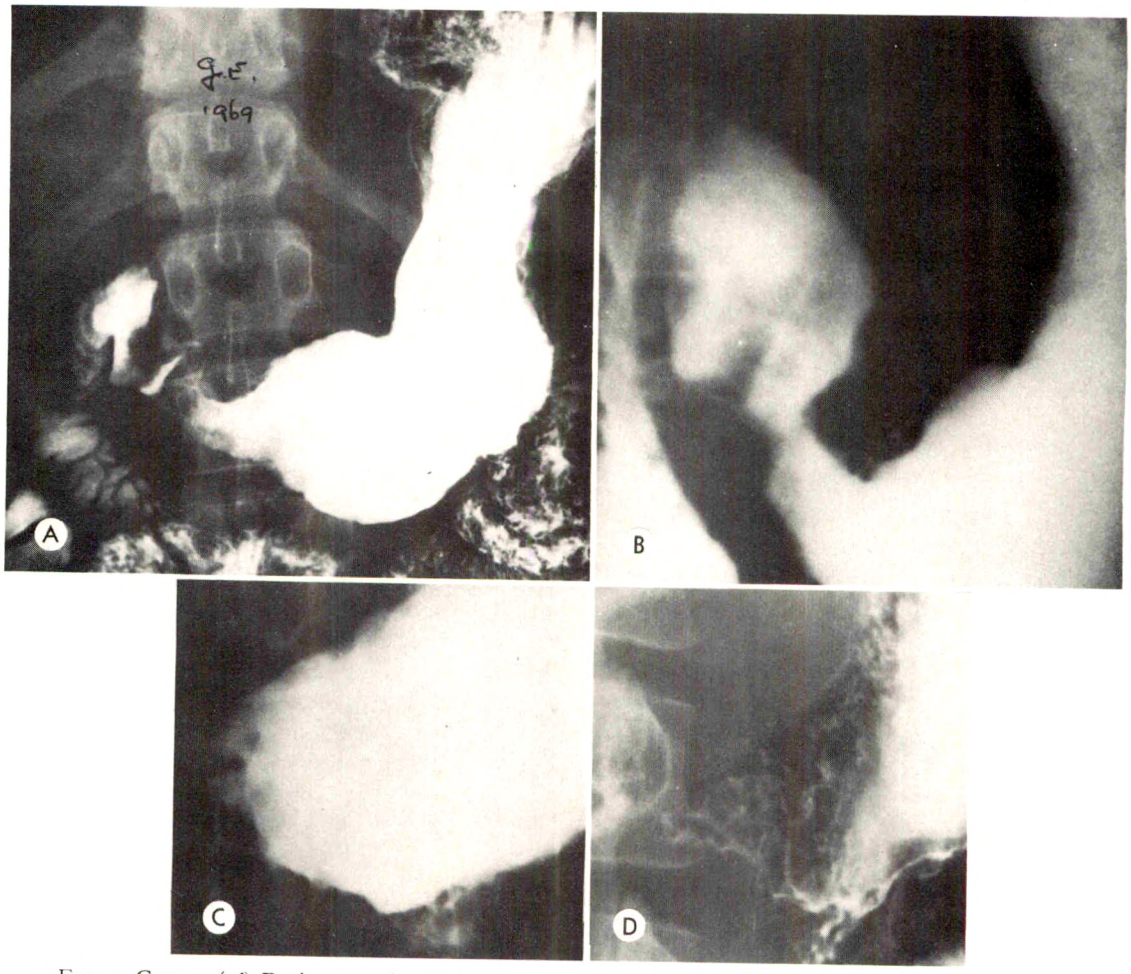

FIG. 2. Case 1. (*A*) Barium meal examination. Antral narrowing with poor distensibility. (*B–D*) Fissured ulceration and cobblestone pattern evident.

tomy was performed together with a vagotomy (Fig. 3). The third part of the duodenum was seen to be compressed by an adhesion, the result of previous surgery.

The patient made an uneventful postoperative recovery and was discharged 12 days later on a full diet and gaining weight.

Pathology. Second Operation: March 3, 1970. The specimen received consisted of a pyloric portion of the stomach and measured roughly 130 square cm. in total area. The thickness varied from 0.6 to 1 cm. The mucosa was granular and ulcerated, especially involving the pyloric mucosa. The ulcers were round to irregular in shape, isolated as well as confluent, resulting in a cobblestone appearance. These were covered by hemorrhagic exudate. There was one 0.4 cm. round ulcer on the lesser curvature. Its clear margin was edematous and the base pale. The ulcer was considered peptic in nature. The serosal surface was unremarkable. No lymph nodes were found in the submitted specimen.

Microscopically, there were large and small ulcers involving the mucosa and submucosa associated with plasma cell and lymphocytic infiltration as well as a few noncaseating granulomas with giant cells. The ulcers also showed a tendency to undermine at the edges and their bases were covered with neutrophil exudate. It was difficult under microscopic observation to determine if any one of these ulcers was peptic in nature. Patchy areas of edema, excess fibrosis and dilatation of capillaries and lymphatics were also noticed. The inflammatory process occasionally involved muscular layers, but did not penetrate the whole thickness of the stom-

ach wall. The serosa was intact (Fig. 4, *A* and *B*).

From the pathologic findings, this is clearly a case of Crohn's disease of the ileocecal region and stomach.

Case II. M.B., a 55 year old woman, was admitted to hospital complaining of crampy abdominal pain of 8 months' duration. The pain was worse after eating and at night and was unrelieved by alkali. During this period there were occasional bouts of diarrhea.

The patient had a history of alcoholism and had biopsy-proven cirrhosis of the liver. Three years previously she had suffered a stroke from which she had made a good recovery.

Physical Examination. The patient appeared well without any evidence of obvious weight loss. Abdominal examination revealed a 3 finger hepatomegaly. Biochemical Findings: Albumin 2.3 mg. per cent; total protein 6.8 mg. per cent.

Upper Gastrointestinal Examination. The esophagus was normal. There was a coarsened "cobblestone" mucosal pattern in the antrum of the stomach which was narrowed, tubular and poorly distensible. In addition, the mucosa of the first and second parts of the duodenum was thickened, edematous and irregular. A 30 cm. long S-shaped segment of jejunum was demonstrated. This was poorly distensible. The adjacent loops were separated from each other and fixed. Horizontal and vertical ulcerations were present within the small bowel (Fig. 5, *A* and *B*).

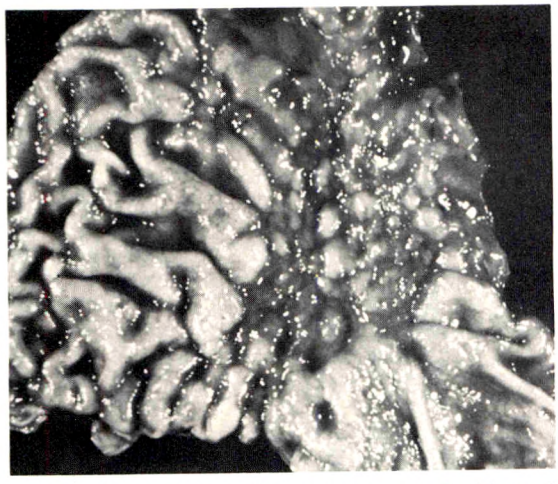

Fig. 3. Case I. Opened resected stomach. Normal gastric mucosa on both sides and coarse pebbly antral disease with fissured ulceration in the center of the specimen.

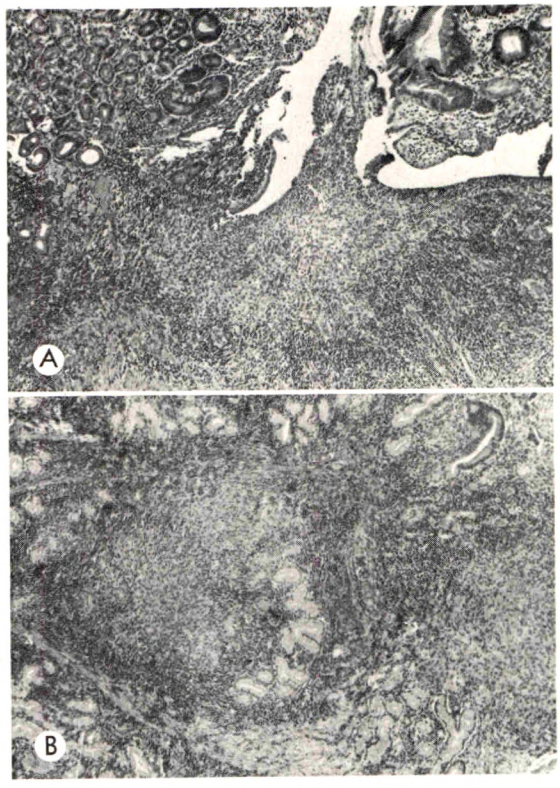

Fig. 4. Case I. (*A*) Mucosal ulceration with aggregate of histiocytes and chronic inflammatory cell infiltration (40×). (*B*) Submucosal noncaseating granulomatous inflammation (40×).

Gastroscopy and duodenoscopy confirmed the coarsened, hyperemic edematous mucosa in the antrum and proximal duodenum. A mucosal biopsy taken from the second part of the duodenum showed nonspecific changes of acute and chronic inflammation. No granuloma was identified.

Case III. R.G., a 19 year old male, was admitted to hospital with a 6 month history of abdominal pain, diarrhea and a 14 pound weight loss. His stools were watery and occasionally blood streaked, and he had up to 5 bowel movements per day.

The patient showed evidence of weight loss, but no other abnormal physical findings. Hematologic Findings: Hematocrit 40.5 per cent; white blood cell count 10,000/cu. mm.; 80 per cent polymorphonuclears; 10 per cent lympho-

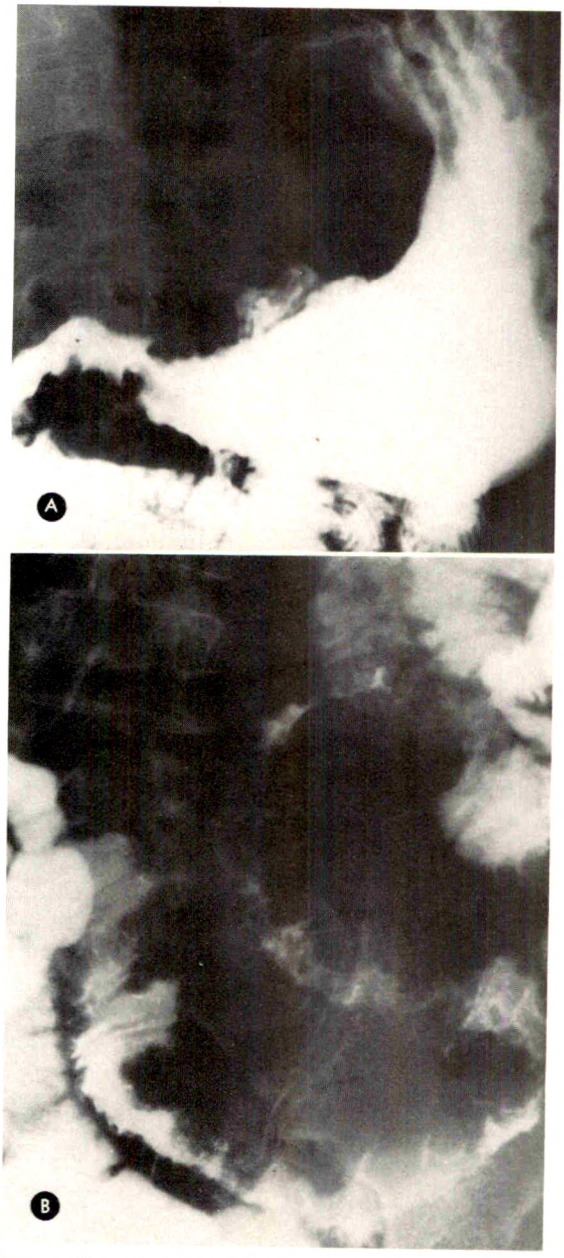

FIG. 5. Case II. (*A* and *B*) Barium meal examination. Coarsened antral mucosa together with thickened, edematous folds of the first and second parts of the duodenum and severe small bowel involvement with fixed and separated loops showing ulceration.

cytes; 2 per cent eosinophils. Chemistry: blood urea nitrogen 15 mg. per cent; creatinine 0.7 mg. per cent; albumin 3.0 mg. per cent; total protein 6.5 mg. per cent.

Upper Gastrointestinal and Small Bowel Examination. Persistent smooth walled conical gastric antral narrowing was present without any evidence of ulceration. The duodenum and proximal small bowel were normal. A thickened and coarsened mucosal pattern together with fissured ulceration were evident in the terminal small bowel. The cecum possessed a conical shape and could not be distended fully (Fig. 6, *A–C*).

CASE IV. M.W., a 23 year old Black female, was admitted to hospital in 1973 with complaints of asthenia, abdominal pain, anorexia and a 40 pound weight loss of 2 months' duration. The patient had experienced episodes of vomiting and diarrhea during this period. Eight years previously, a laparotomy at another hospital had revealed a pelvic abscess. Segmental resection of the small bowel was performed at that time.

A tender abdominal mass measuring 15 cm. ×8 cm. was palpated in the umbilical region extending to the left of the midline. Hematologic Data: Hemoglobin 11.4 gm. per cent; hematocrit 34 per cent; white blood cell count 10,300/cu. mm.

Roentgen Finding. Chest roentgenogram normal. Abdominal roentgenogram normal. Barium enema examination: Segmental colitis was present involving the cecum, ascending colon and transverse colon with fissured ulceration, loss of normal haustral pattern, limited distensibility and a coarsened mucosa. The terminal small bowel showed similar changes. Upper gastrointestinal and small bowel examination: The stomach was tubular and narrowed. Thick prominent antral folds were present on the greater curvature. Peristalsis was poor and sluggish (Fig. 7, *A* and *B*).

Gastroscopy and duodenoscopy were performed. There was marked abnormality of the antrum and body of the stomach. The mucosa was elevated, irregular and appeared inflamed and friable. The duodenal bulb and descending duodenum were normal. Gastric biopsy revealed the inflammatory changes consistent with subacute gastritis, but no granulomas were identified.

The patient was placed on parenteral hyperalimentation, Azulfidine 1 gm. q.i.d., vitamin supplements and antispasmodics. After a stormy hospital course, the abdominal mass resolved and the patient improved. A subsequent upper gastrointestinal series and barium enema examination showed considerable improvement

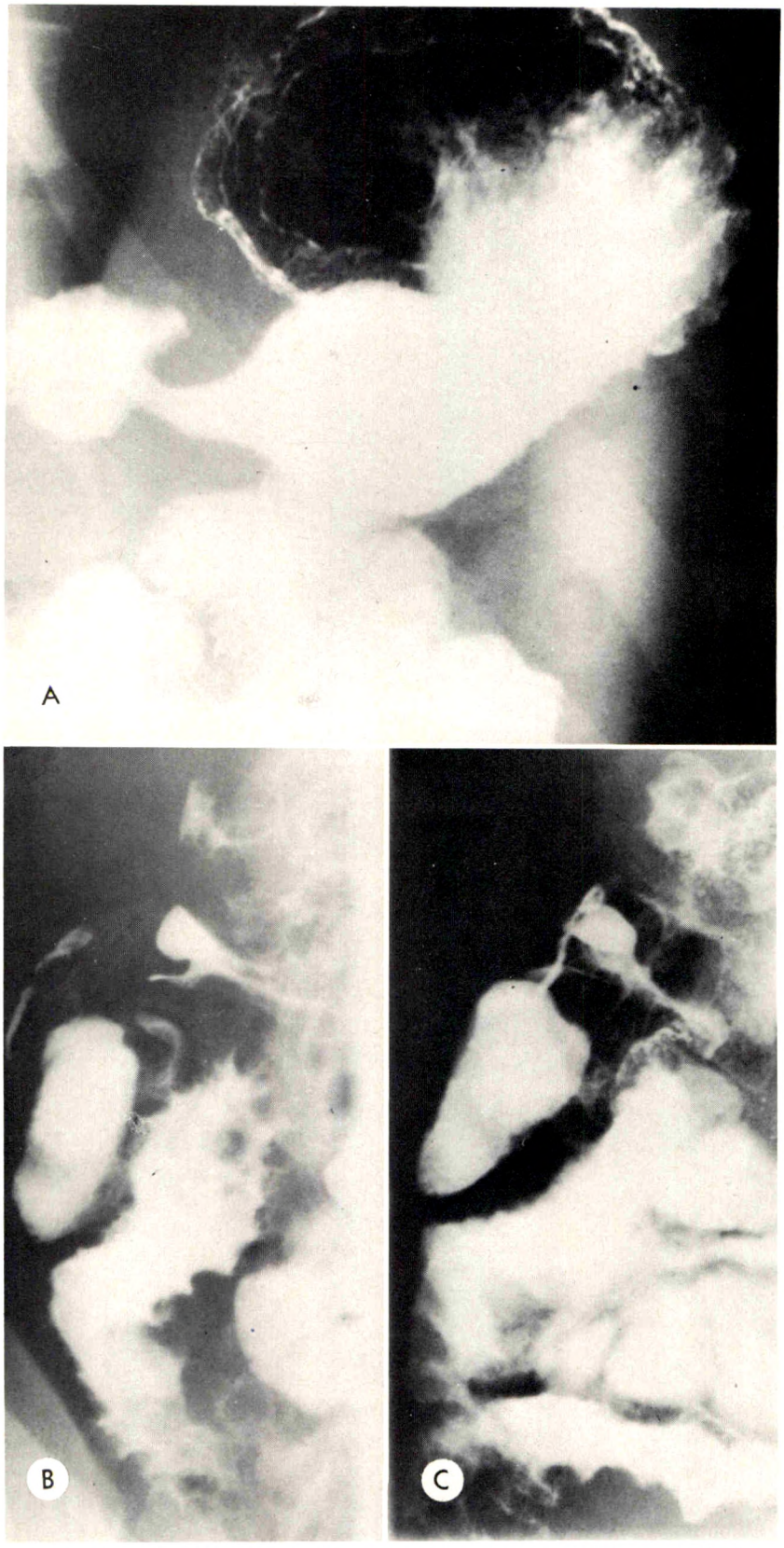

FIG. 6. Case III. (*A–C*) Barium meal and small bowel series. Persistent conical antral narrowing of stomach and severe ileocecal Crohn's disease.

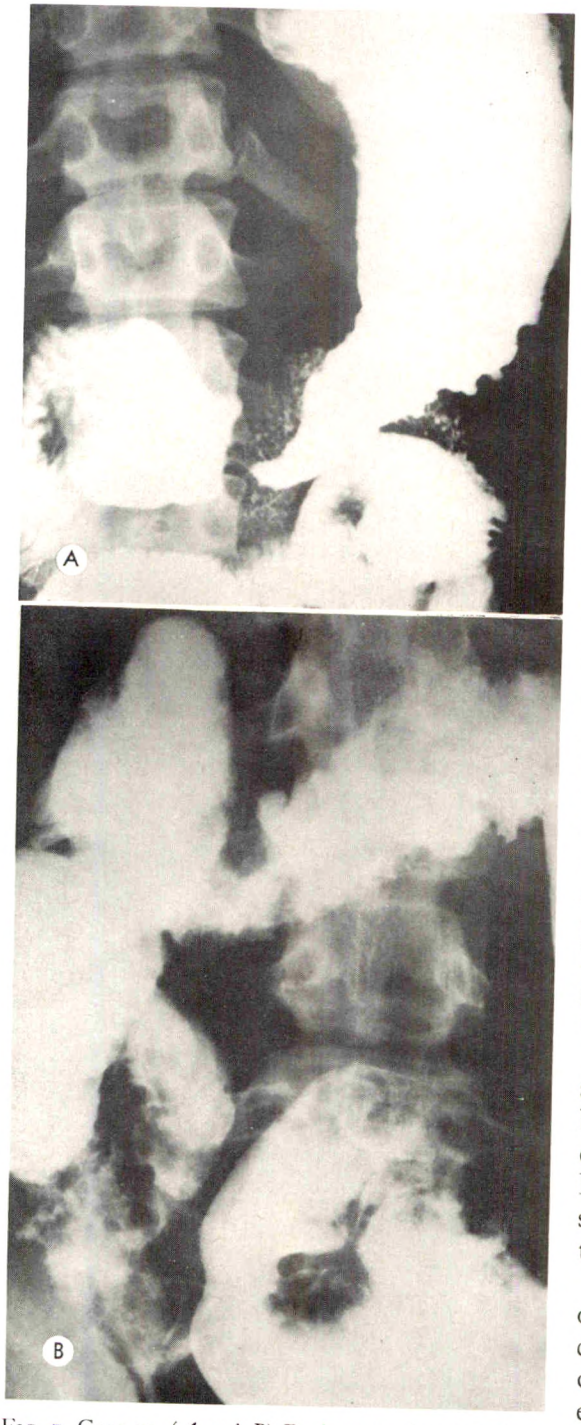

FIG. 7. Case IV. (*A* and *B*) Barium meal and barium enema examination. "Ram's horn" deformity of antrum with poor distensibility and irregular coarse mucosal folds along the greater curvature. Extensive Crohn's disease of the terminal ileum, cecum and transverse colon is present.

in the appearance of the small bowel and colon, but the stomach remained unchanged.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of the gastric deformity would include infiltrative processes which can produce a rigid stomach wall and so limit its full distensibility. Scirrhous carcinoma causing a "leather bottle" appearance may be difficult to exclude on roentgenologic grounds alone. In Crohn's disease, however, peristalsis is present, although sluggish. Fully one-third of the patients with Crohn's disease of the stomach who underwent surgery were operated on because an infiltrating carcinoma could not be excluded on roentgenologic grounds alone.[14]

Chronic peptic ulceration with healing by fibrosis frequently produces antral deformity and the deformity itself may be further aggravated when a pseudolymphomatous reaction results from chronic gastric ulceration.[8] It then remains for the pathologist to determine that the lymphocytic infiltration of the stomach wall is the result of peptic ulceration with an unusual response and not a true lymphoma. Lymphoma may produce a similar roentgenologic appearance on occasion, and certainly gastric narrowing may be seen after radiation therapy for gastric lymphoma.

Corrosive gastritis tends to narrow the antrum, and both acids and alkalis have been responsible for the roentgenologic changes which have been produced.[17] Rarely, syphilis and tuberculosis affect the stomach and produce abnormalities akin to those described.[8]

Other infiltrative processes include eosinophilic gastroenteritis and gastric amyloidosis.[4,8] This last abnormality occurred as a complication of severe granulomatous disease in 1 of our patients. The patient had had Crohn's disease for many years and with the development of renal failure, renal and rectal biopsies were performed which proved the presence of amyloidosis in both sites.

The pure antral deformity in this patient was more consistent with the diagnosis of Crohn's disease than secondary amyloidosis, which would tend to involve the entire stomach.

DISCUSSION AND CONCLUSIONS

The propensity for the antrum to be involved when Crohn's disease affects the stomach results in inflammatory changes which produce the tubular shape with conical narrowing. The stomach consequently distends poorly and peristalsis is both sluggish and infrequent. This "ram's horn" configuration was readily recognizable and was seen in 9 of our 12 patients. Two other patients had pyloroduodenal deformity and 1 patient, a child, showed irregular, abnormal coarse antral mucosal disease.

Gastric dilatation which resulted from pyloroduodenal stenosis was a significant finding in 2 cases (Fig. 8, *A* and *B*). The marked dilatation of the stomach which occurs in longstanding obstruction, either from antral carcinoma or chronic peptic ulceration, was not seen.

In 3 patients there was excess retained secretion in the stomach.

The gastric mucosa possessed a variable pattern, ranging from a coarsened, pebbly appearance to a smooth wall suggesting atrophy. Superficial gastric ulceration due to Crohn's disease and seen on endoscopy was not always confirmed on barium enema studies because of the shallow nature of the ulceration.

The severe pyloroduodenal deformity resembles peptic ulcer disease and is likely to be regarded as responsible for the abnormality in the absence of confirmatory signs of Crohn's disease elsewhere in the gastrointestinal tract. The history may not always be helpful, especially where diarrhea

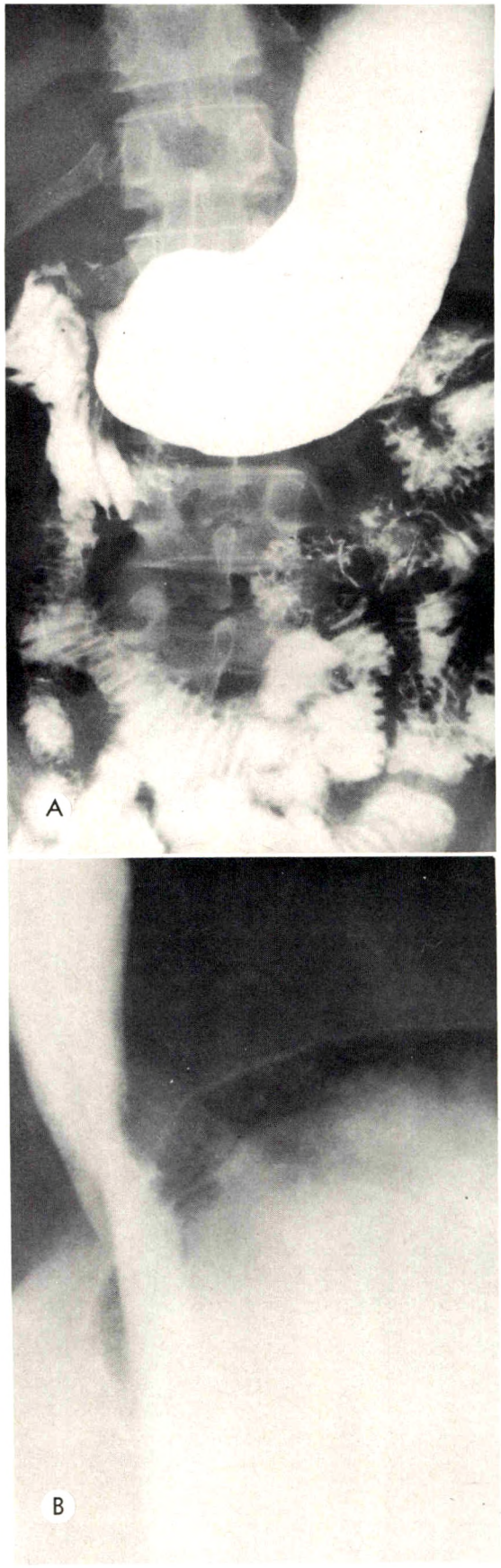

FIG. 8. (*A* and *B*) Barium meal examination. Pyloroduodenal deformity with narrowing and moderate gastric dilatation. Severe Crohn's disease of the duodenum and small bowel is evident. The rigidity and deformity of the lateral esophageal wall is apparent.

is minimal and the patient's bowel symptoms are overshadowed by dyspepsia.

As with small bowel and colonic involvement, the appearance of gastric Crohn's disease is dependent not only upon the severity of involvement but also the stage of the disease. Thus, at varying times, the appearance may include: (1) "cobblestoning;" (2) fissured ulceration; (3) atrophic mucosa; or (4) stenosis.

Gastroscopy is extremely useful in confirming the roentgenologic findings and is of paramount importance in excluding malignancy. Biopsy performed by the endoscopist usually shows nonspecific gastritis only, presumably due to the superficial specimen obtained.

The lack of precise histology of Crohn's disease should not dissuade the clinician from this diagnosis if the clinical and roentgenologic evidence are strong.

The roentgenologic appearance of Crohn's disease includes:

(1) A smooth tubular antrum which is poorly distensible and exhibits sluggish peristalsis (9 patients).
(2) Coarse "cobblestone" antral folds with fissured ulceration (3 patients).
(3) Pyloroduodenal deformity with moderate outlet obstruction (2 patients).
(4) Excess gastric secretions (3 patients).
(5) Crohn's disease elsewhere in the gastrointestinal tract (12 patients).

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REGIONAL ENTERITIS OF THE DUODENUM*

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REGIONAL enteritis is a protean disease which may involve the entire gastrointestinal tract. When the duodenum is involved, it usually occurs after longstanding disease has been present in the small bowel or colon. Occasionally, the duodenum may be the site of initial involvement or be involved concurrently with the small bowel and/or colon. Certain roentgenographic manifestations are strongly suggestive of Crohn's disease, even when the changes are present in an unusual location. Their recognition is especially important since the referring physician may not suspect regional enteritis.

The purpose of this paper is to emphasize that regional enteritis of the duodenum is more common than has been realized and to discuss the characteristic roentgen features of this entity.

MATERIAL AND METHOD

Of the 312 patients with regional enteritis seen at Duke University Medical Center and the Durham Veterans Administration Hospital between 1965 and 1973, there were 23 patients (7 per cent) with duodenal regional enteritis. One patient presented initially with isolated duodenal involvement and 2 years later developed changes in the terminal ileum. Six patients had concomitant involvement in the duodenum and small bowel. The remaining 16 patients developed duodenal regional enteritis after involvement of the ileum and/or colon had been well documented.

Sixteen of the 23 patients underwent a surgical procedure. All of these patients had histologic evidence of Crohn's disease.

Roentgenograms of the upper and lower gastrointestinal tract were available in each patient, and the diagnosis of Crohn's disease was made by the characteristic roentgenographic features. In 7 patients the stomach was involved in continuity with the duodenum.

CLINICAL FINDINGS

Abdominal pain and diarrhea occurred in 22 of the 23 patients. Sixteen had evidence of gastric outlet obstruction manifested by vomiting and post-prandial fullness. In 4 of the 16, gastric emptying procedures were required to relieve gastric outlet obstruction.

None of the 23 patients had severe gastrointestinal hemorrhage, but 7 were anemic. There was significant weight loss in 16 patients.

Six patients were referred to the Radiology Department with a clinical diagnosis of peptic ulcer disease. All of these patients had changes which were thought characteristic of regional enteritis, and in 5, small bowel contrast examinations showed Crohn's disease in the terminal ileum. The sixth was the 1 patient who had regional enteritis of the duodenum as an isolated finding but subsequently developed changes in the small bowel (Fig. 1, *A* and *B*).

Seven patients who showed changes in the duodenum had no evidence of upper gastrointestinal symptoms other than occasional upper abdominal pain. All of these patients had intermittent diarrhea and roentgenographic changes of regional enteritis in the small bowel. One patient died from complications of regional enteritis after undergoing multiple surgical procedures, which included a gastrojejunostomy.

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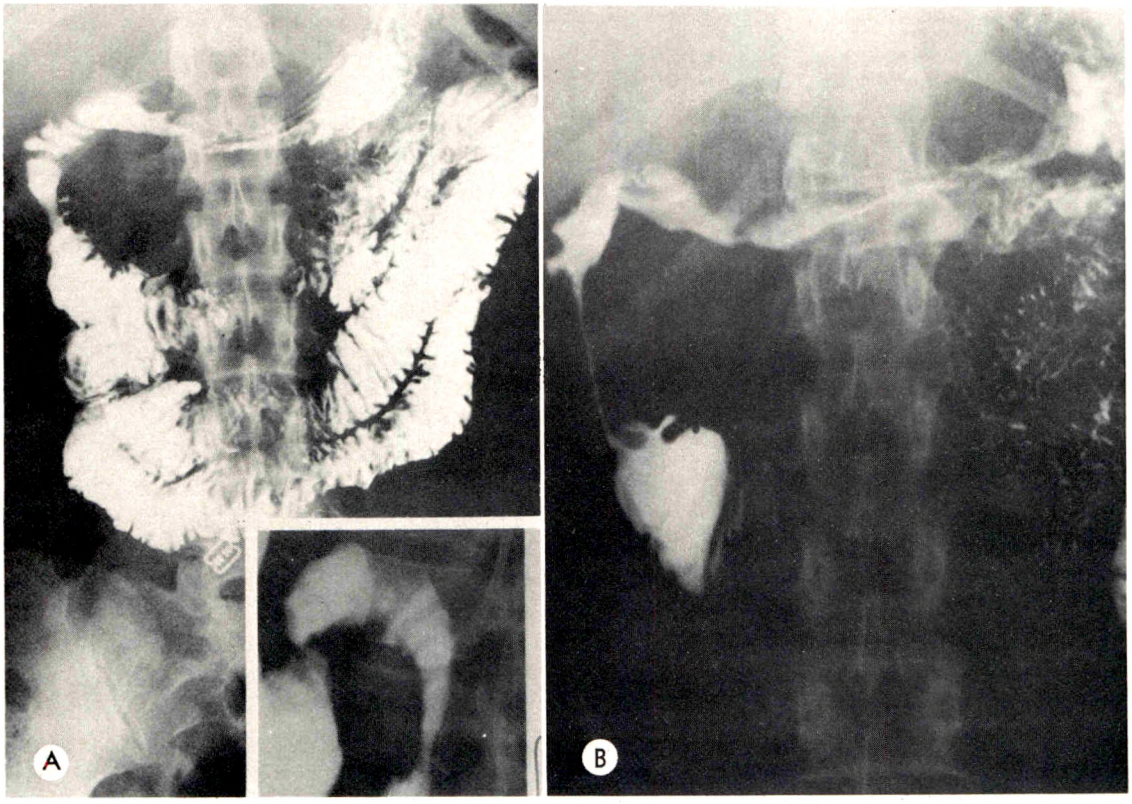

Fig. 1. (*A*) Roentgenogram in 1969 of a 22 year old female who presented with symptoms of peptic ulcer disease and gastric outlet obstruction. There is distortion of the duodenal bulb and second portion of the duodenum with thickening and disorganization of the mucosal folds, pseudodiverticula, and smooth stenosis with abrupt transition to normal mucosa. A small bowel examination was normal. (*B*) Roentgenogram 3 years later shows progression to classic string sign. The terminal ileum was involved at this time.

This was the only death in the 23 patients.

ROENTGENOGRAPHIC FINDINGS

All 23 patients ultimately had the characteristic changes of Crohn's disease involving the terminal ileum and/or colon. Both the non-stenotic and stenotic forms of regional enteritis were demonstrated in the duodenum. In general, the roentgen appearance was similar to regional enteritis of the small intestine. In 7 patients there was concurrent gastric involvement; in all of these, the changes were in the antrum and extended across the pylorus to the first and second portions of the duodenum. A duodenocolic fistula was demonstrated in 1 patient (Fig. 9).

In the late stages of duodenal Crohn's disease, the roentgenographic findings are frequently quite specific. The string-sign, which was initially described in the terminal ileum, is one of the classic roentgenographic abnormalities in regional enteritis which has been recognized by radiologists for decades. It can occur in the duodenum (Fig. 1*B*). The string-sign is not always indicative of the caliber of the lumen.[14] As in the terminal ileum, serial roentgenograms will show the diseased segment to vary in caliber.

The second portion of the duodenum seems to be the most common site of involvement by Crohn's disease. The most typical abnormality is a smooth tubular

TABLE I

ROENTGENOLOGIC FINDINGS IN DUODENAL CROHN'S DISEASE

A. *Early*
1. Blunted, thickened and disorganized mucosa
2. Moderate narrowing and spasm
B. *Late*
1. Effacement-loss of mucosal pattern
2. Pseudodiverticula
3. Ulceration-cobblestone appearance
4. Stenosis
a. moderate to severe—obstruction
b. associated with spasm—string sign
c. strictures—single or multiple
d. located at apex of duodenal bulb
e. skip areas
5. Pseudopost-Billroth I sign—most characteristic
6. Fistula—usually from colon or small bowel

stenosis. Table 1 lists the roentgenographic abnormalities encountered in regional enteritis of the duodenum.

A. EARLY CHANGES

Early in the disease, the involvement of the duodenum is more subtle and less specific than the appearance of advanced regional enteritis. These early changes are manifested by blunted, thickened, edematous folds which become disorganized and on occasion may assume a polypoid or nodular appearance, possibly due to hyperplastic mucosa[14] (Fig. 2*A*; 6*A*; and 7*A*). In many cases the mucosa will coat poorly, and mild narrowing with some spasm will be noted.

B. LATE CHANGES

Loss of Mucosa-Pseudodiverticula: As the disease progresses, the mucosal folds become more thickened and fixed: in some cases there is effacement and loss of the normal mucosal pattern (Fig. 6*B*). Small crypts or pouches (pseudodiverticula)[14] are frequently demonstrated in these areas of thickened mucosa. This phenomenon is usually associated with narrowing of the lumen of the duodenum (Fig. 1*A*; and 2, *A* and *B*). These crypts or pouches are not usually numerous and probably represent ulcerations or mucosal pouches between more markedly narrowed segments. When these are small and numerous, as well as localized to one portion of the duodenum, they can closely resemble multiple diverticula. Deep penetration or perforation of these small crypts or ulcers in the small bowel may lead to fistula formation.[14] Fistula formation is a rare occurrence in the duodenum and will be mentioned later.

Ulceration-Cobblestone Formation: Ulcerations in duodenal Crohn's disease are difficult to demonstrate and may be impossible to definitely separate from the pseudodiverticula mentioned above. Occasionally, a nodular appearance will be encountered, but overt cobblestoning, which has been described in the small bowel and colon, has not been described frequently in the duodenum. It was not recognized in the present series. In some cases the mucosa may appear destroyed, which is a characteristic feature of malignancy. However, there will be some change in caliber of the lumen, and the abnormalities in the colon or small bowel will help distinguish regional enteritis from carcinoma.

Stenosis-Obstruction: As the changes progress, the mucosal folds become obliterated and the duodenum becomes rigid and stiff, finally progressing to a smooth, tapered stenosis (Fig. 1, *A* and *B*; 3; 4; 5; 7*B*; and 8*B*). Consequently, dilatation of the stomach and/or duodenum proximal to the stenosis may occur (Fig. 4; 5; and 7, *A* and *B*). When the stenosis is severe, surgical intervention may be required for relief of the obstruction. If the changes have not evolved to severe stenosis, medical therapy may stop the progressive involvement and even allow improvement in the lesions (Fig. 5). Skip areas of stenotic involvement are sometimes visible in the duodenum and upper jejunal loops;[14] however, they were not encountered in this series.

Stenosis at Apex of Duodenal Bulb: Regional enteritis may initially involve the apex of the duodenal bulb and adjacent second portion of the duodenum without simultaneous involvement of the pylorus

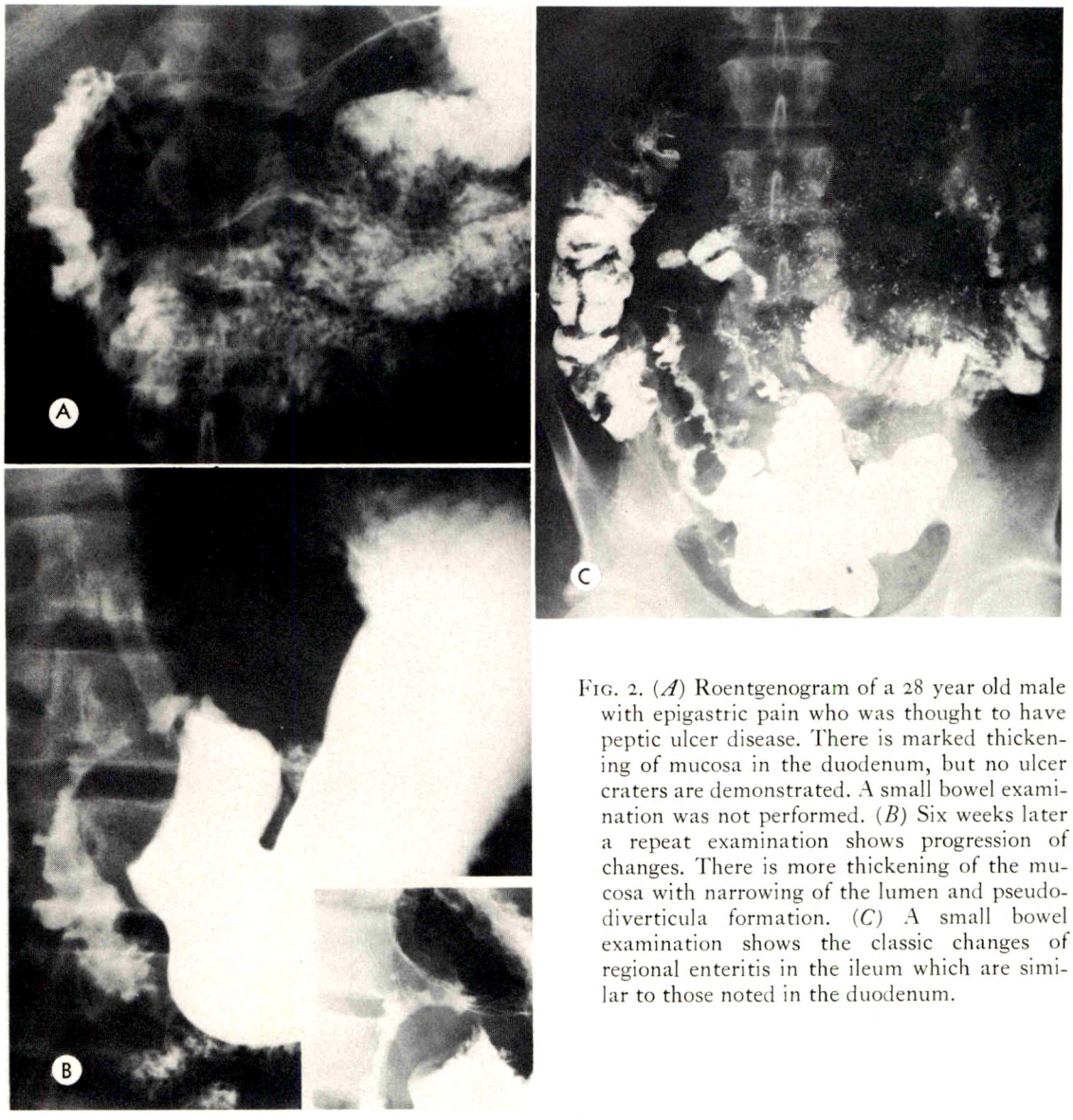

Fig. 2. (*A*) Roentgenogram of a 28 year old male with epigastric pain who was thought to have peptic ulcer disease. There is marked thickening of mucosa in the duodenum, but no ulcer craters are demonstrated. A small bowel examination was not performed. (*B*) Six weeks later a repeat examination shows progression of changes. There is more thickening of the mucosa with narrowing of the lumen and pseudodiverticula formation. (*C*) A small bowel examination shows the classic changes of regional enteritis in the ileum which are similar to those noted in the duodenum.

and antrum. This produces a characteristic feature of Crohn's disease which enables it to be distinguished from the typical inflammatory scarring due to peptic ulcer disease. A smoothly tapered, funnel shaped narrowing of the apical portion of the duodenal bulb is noted in contrast to the lobulated, irregular, clover-leaf type deformity so characteristic of peptic ulcer disease (Fig. 6*B*). Additionally, with post-bulbar ulcers, an incisura is characteristically demonstrated. This incisura will not be present in regional enteritis.

Pseudopost-Billroth I Sign: The most characteristic roentgenographic finding of Crohn's disease involving the duodenum occurs when the antrum, pylorus, and duodenal bulb are blended into a single tubular or funnel shaped structure. The normal anatomic landmarks between the antrum and second portion of the duodenum are obliterated (Fig. 7*B*; and 8*B*). This deformity has been labeled the pseudopost-Billroth I sign by Nelson.[14] This type of deformity was present in 5 of the 23 patients in the present series. The appearance does suggest

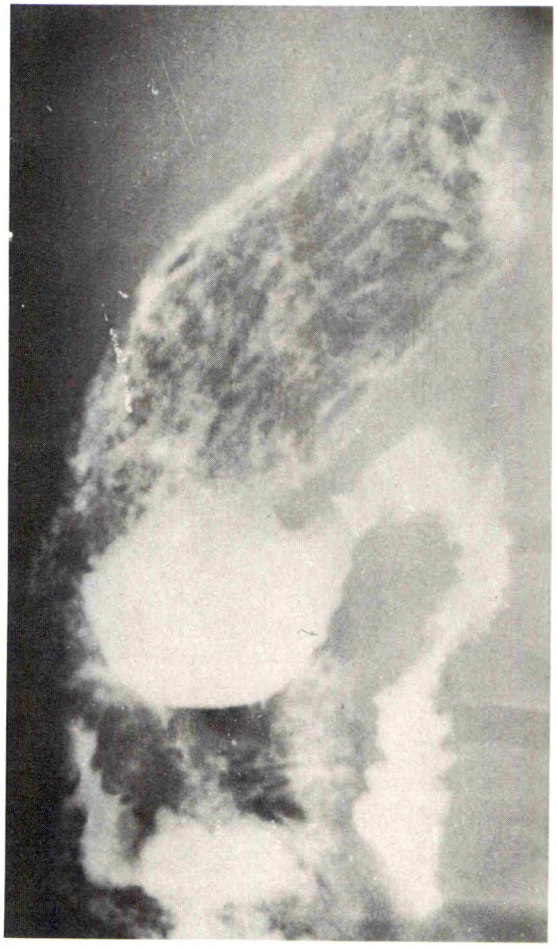

FIG. 3. Patients with regional enteritis of the duodenum usually develop the changes after the disease has been established in the small bowel or colon.

Roentgenogram of a 16 year old male with a 5 year history of regional enteritis who had a right colectomy with an ileotransverse colostomy at the age of 14. Edematous thickened mucosa in the duodenum with a suggestion of antral involvement is demonstrated. The duodenum was normal 5 years earlier.

an inflammatory lesion, in contrast to gastric or duodenal neoplasms which rarely cross the pylorus. In regional enteritis there is some pliability and distensibility of the antrum; the mucosa at each end of the lesion often has a shaggy nodular appearance but is not destroyed as in neoplastic disease. There is usually a smooth but obvious transition from the normal gastric antrum proximal and the normal duodenum distal to the diseased segment. In gastric or duodenal carcinoma, the transition between normal and diseased mucosa is more abrupt. When the pseudopost-Billroth I deformity is encountered, the diagnosis may be confirmed with small bowel and colon examinations which will show the classic changes of Crohn's disease.

Fistula: Some authors have reported that duodenal fistulae do not occur in patients with regional enteritis of the duodenum.[7,17] This is not correct. Nelson[14] described a duodenocolic fistula causing a blind loop syndrome in 1 patient, and Legge *et al.*[13] reported reflux of barium into the pancreatic and biliary ducts which they believed could be due to fistula formation. Usually, duodenal fistulae are secondary to involvement in either the small bowel or the colon; the most common combination is from the transverse colon to the second portion of the duodenum (Fig. 9). Primary duodenal fistulae originating in the duodenum are uncommon. However, the presence of a duodenal fistula associated with abnormal

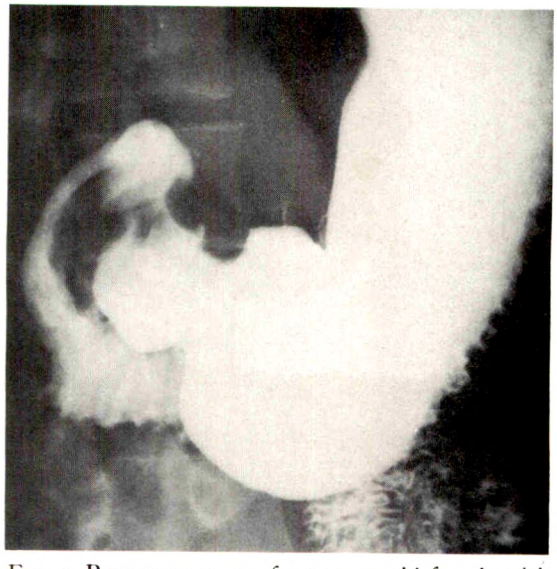

FIG. 4. Roentgenogram of a 20 year old female with a clinical history suggesting peptic ulcer disease. There is a smooth stricture in the immediate postbulbar region. Nodular mucosa is noted at the distal portion of the abnormal segment. The duodenal bulb and duodenum distal to the diseased area are normal. A small bowel examination showed classic changes of regional enteritis in the ileum.

mucosa certainly should bring to mind the possibility of duodenal Crohn's disease.

DISCUSSION

Only 124 cases of duodenal Crohn's disease have been described in the literature.[15] However, the number of reported cases has more than doubled in the past 5 years. The incidence is stated to be between 1 and 4 per cent,[5,7] which is lower than the 7 per cent incidence reported in this series. It is apparent that duodenal involvement with Crohn's disease is more common than has been previously noted. There are 2 reasons for this: (1) some cases are not diagnosed because of unfamiliarity with the condition; and (2), there is difficulty in obtaining specimens for pathologic verification.

As in the terminal ileum, a diagnosis of duodenal regional enteritis is justified by a combination of clinical data associated with the characteristic roentgenographic findings.[2] Documentation of Crohn's dis-

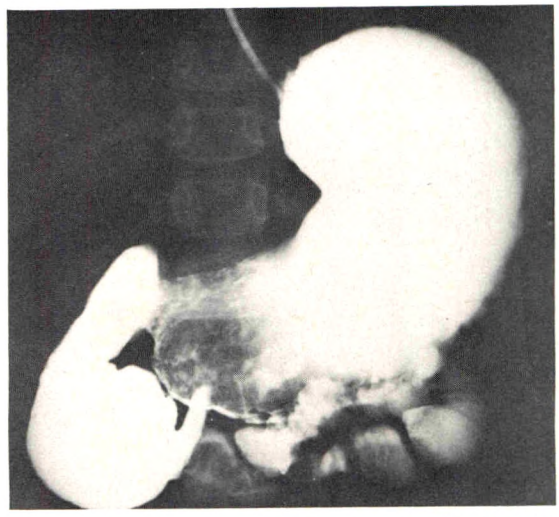

Fig. 5. Roentgenogram of a 9 year old Black male who presented with nausea, vomiting, and bloody diarrhea. There is a stricture in the third portion of the duodenum with proximal dilatation and partial obstruction. Barium examinations of small bowel and colon showed characteristic changes of regional enteritis. After 6 weeks, there was clinical and roentgenographic improvement with medical therapy.

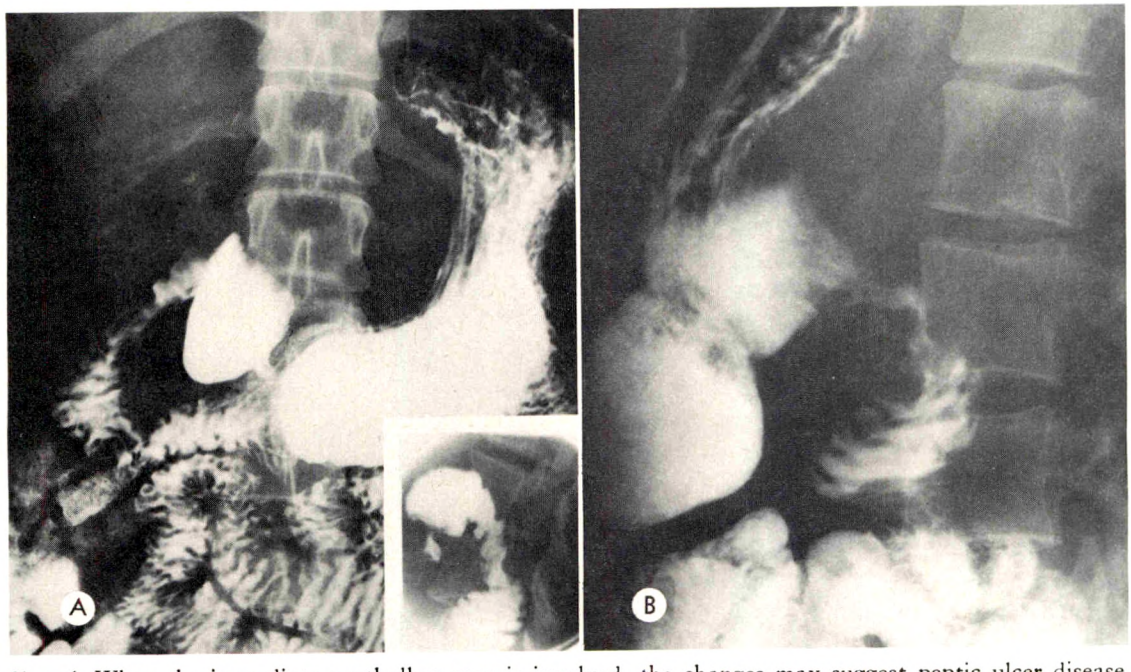

Fig. 6. When the immediate postbulbar area is involved, the changes may suggest peptic ulcer disease. (*A*) Roentgenogram of a 24 year old female who presented with a 3 month history of diarrhea and epigastric pain accentuated by food. There is narrowing of the lumen in the immediate postbulbar area with thickened edematous mucosa. Obvious changes of regional enteritis in the terminal ileum were demonstrated. The patient underwent a partial ileocolectomy. (*B*) Roentgenogram 2 years later shows more narrowing of lumen and loss of normal mucosal folds without obvious ulceration.

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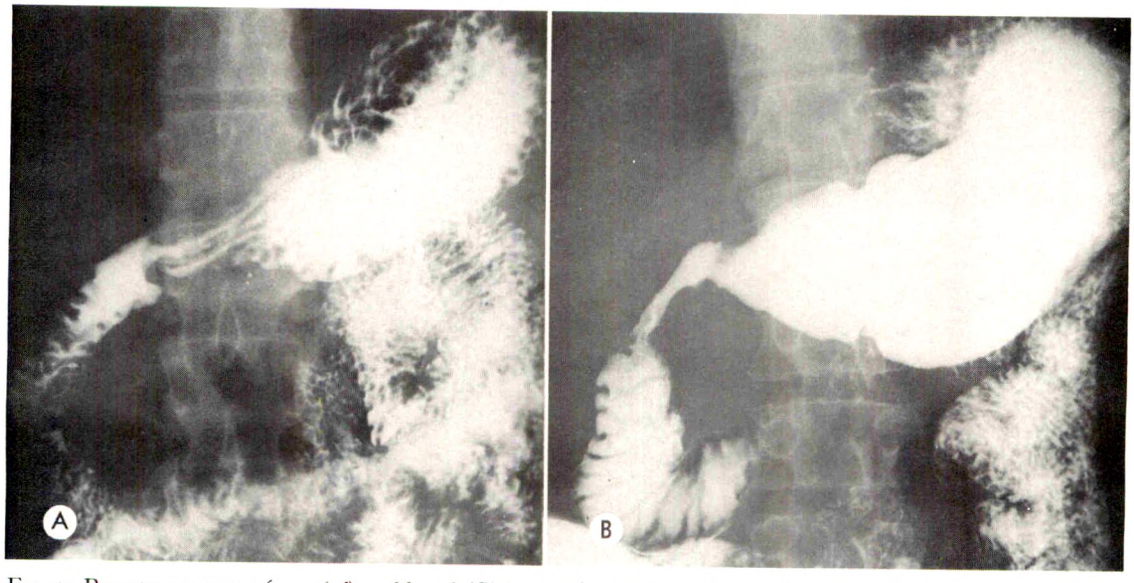

FIG. 7. Roentgenograms from (*A*) 1966 and (*B*) 1972 of a young male who had a total colectomy in 1969 for regional enteritis. The study in 1966 shows a suggestion of thickened folds in the second portion of the duodenum. The study from 1972 shows that the antrum, pylorus, and duodenal bulb blend into one continuous tubular structure with loss of normal anatomic landmarks (pseudopost-Billroth I sign).

ease in the small bowel or colon certainly aids in establishing the suspected diagnosis of duodenal Crohn's disease. Using these criteria the diagnosis was established in all 23 patients in this series.

The clinical findings in the 23 patients do not differ significantly from those reported by others.[1,4–7,9,10,12,16,17] Comfort and coworkers[3] were the first to point out that patients with duodenal Crohn's disease experience continuous intermittent abdominal pain aggravated by food, a weight loss, and diarrhea. These symptoms may not be present in all patients with duodenal Crohn's disease. In fact, severe stenosing duodenal lesions may be associated with a paucity of symptomatology. However, when a young patient presents with symptoms of atypical peptic ulcer disease associated with gastric outlet obstruction and diarrhea, the possibility of Crohn's disease with duodenal involvement should be considered.

Although severe upper gastrointestinal hemorrhage has occurred in patients with regional enteritis involving the stomach and duodenum,[11,15] this was not encountered in the present series. Seven patients were anemic, which is in keeping with other reports.[1,17]

Legge *et al.*[13] reported associated pancreatitis in 3 of 10 patients with regional enteritis of the duodenum, all of whom had reflux of contrast medium into the biliary and pancreatic ducts demonstrated by upper gastrointestinal examinations. Dobrilla[4] indicated that pancreatitis can occur in patients with regional enteritis who do not have duodenal involvement and suggested that there may be an inter-relationship between regional enteritis and pancreatitis even when the duodenum is not involved. Pancreatitis was not encountered in the present series and has been infrequent in other series.[1,4–7,9,10,16,17]

Fielding and Cooke[8] reported an incidence of peptic ulceration of 10 per cent in patients with Crohn's disease. They postulated that this was secondary to increased acid output in patients who had undergone small bowel resections. None of the patients in the present study had demonstrable gastric or duodenal ulcers, which is in agreement with other reports.[1,3,5,6,9,12,17]

the unsuspecting clinician. Peroral biopsy techniques are rarely adequate for histologic confirmation of Crohn's disease. Therefore, roentgenographic data form the basis for diagnosing and treating patients with regional enteritis.

SUMMARY

Regional enteritis involves the duodenum more commonly than has been suspected.

The demonstration of tubular narrowing of the antrum, pylorus, duodenal bulb, and second portion of duodenum is almost pathognomonic of the disease.

Any inflammatory change of the duodenal loop in the absence of clinical pancreatitis warrants consideration of the diagnosis of regional enteritis and complete evaluation of the gastrointestinal tract. Patients with duodenal involvement will usually have the more easily recognizable changes in the small bowel and/or colon.

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DUODENAL PSEUDOPOLYP—THE FLEXURE FALLACY*

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IN the past few years, 4 patients with a persistent roentgenographic contour defect at the superior flexure of the duodenum have had exploratory surgery at the San Francisco General Hospital and the University of California, San Francisco. In each case, the only positive operative finding was prominence of mucosal folds in the proximal duodenum. In 2 cases, full thickness biopsy revealed normal duodenum, and in 2 cases biopsy was not performed.

In all 4 of these cases the surgery was elective and was prompted by repeated roentgenographic observation of a persistent contour abnormality on the concavity of the superior duodenal flexure (Fig. 1, *A–D*). In all patients the observation was made on at least 2 upper gastrointestinal examinations, and in 2 patients the abnormality was also demonstrated with hypotonic duodenography. Surgery was performed 1 to 17 days after the final gastrointestinal series. No patient had any evidence of an active ulcer crater or mucosal scarring at the site of the roentgenographic abnormality.

Since our original report of this "pseudopolyp,"[4] we have been informed of several other patients with identical findings who have undergone negative duodenal exploration, and, therefore we believe that this entity should be illustrated and reported.

MATERIAL

Following analysis of our initial 4 surgically explored cases, we have examined many other patients with similar roentgenographic findings (Fig. 2, *A* and *B*; 3, *A–D*; and 4). Follow-up varied from 6 months to 15 years, and no patient has developed significant duodenal disease. Three identical cases from the Massachusetts General Hospital in Boston, all with a minimum of 3 years follow-up, have a similar clinical course. From this series we have concluded that this is a rather common phenomenon which can occur in a broad age range, in both males and females.

A typical case, with endoscopic findings, is illustrated in Figure 5, *A–D* and Figure 6, *A* and *B*. The characteristic filling defect is seen. It was accentuated by graded pressure over the bulb. At duodenoscopy there were prominent folds in the duodenal bulb (Fig. 6*A*) with no evidence of ulcer or mucosal erosion. The descending duodenum was normal (Fig. 6*B*).

DISCUSSION

Several roentgenographic maneuvers can help to establish the benign nature of this finding. Occasionally the lesion can be effaced during hypotonic duodenography. Good air contrast studies will sometimes outline definite redundant mucosal folds. The mass-like effect is accentuated by pressure and by contraction of the descending second portion of the duodenum.

The explanation for this phenomenon appears to be a heaping up of redundant loose mucosa on the inner aspect of the duodenal flexure. As the tubular muscle wall of the gut turns, the outer mucosa is stretched while the inner folds at the flexure are compressed and pile up. A similar occurrence may sometimes be observed in the lower duodenal flexure or other parts of the gut.

Recently, additional evidence has been

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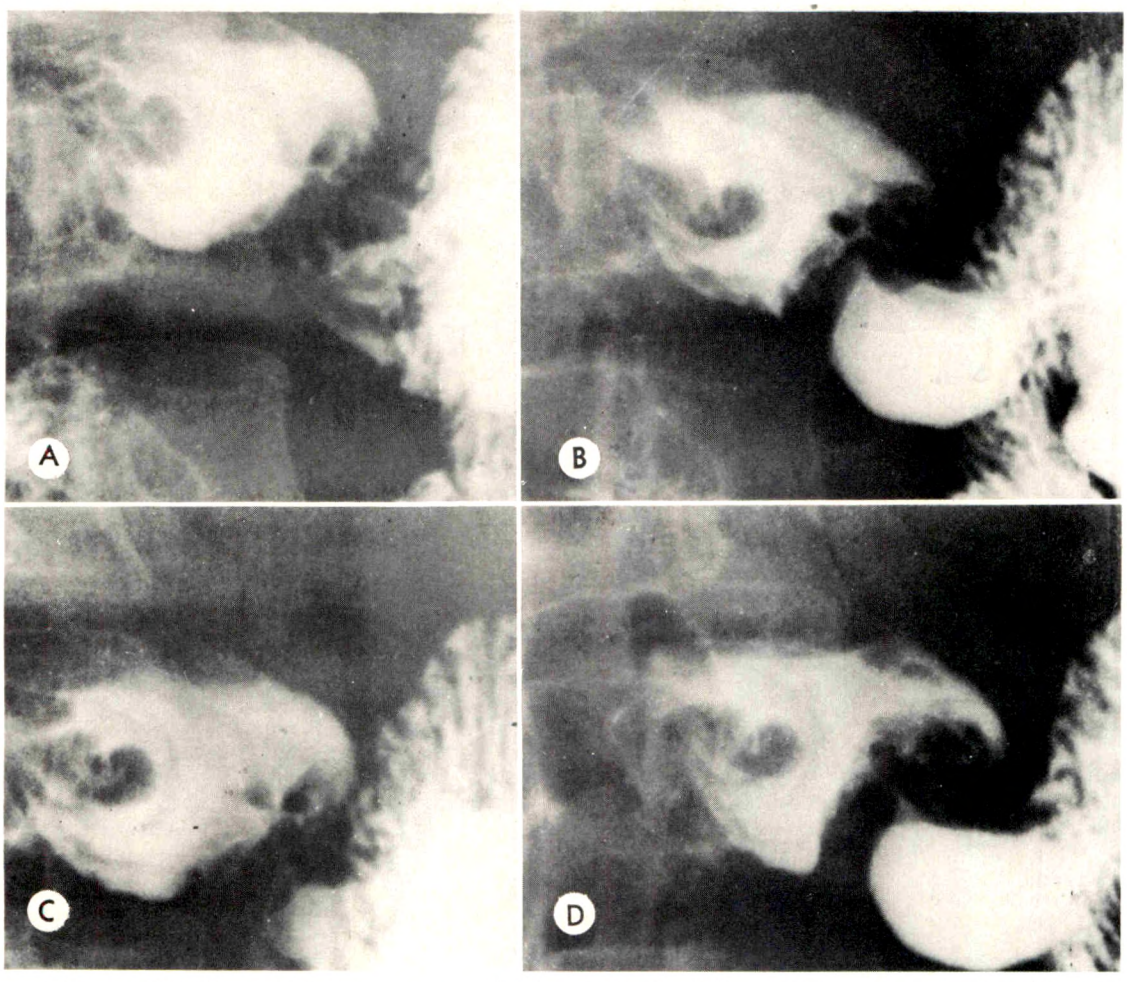


FIG. 1. (*A–D*) Four spot roentgenograms showing a negative filling defect on the concavity of the superior duodenal flexure. At operation, 2 days later, normal duodenal folds were identified.

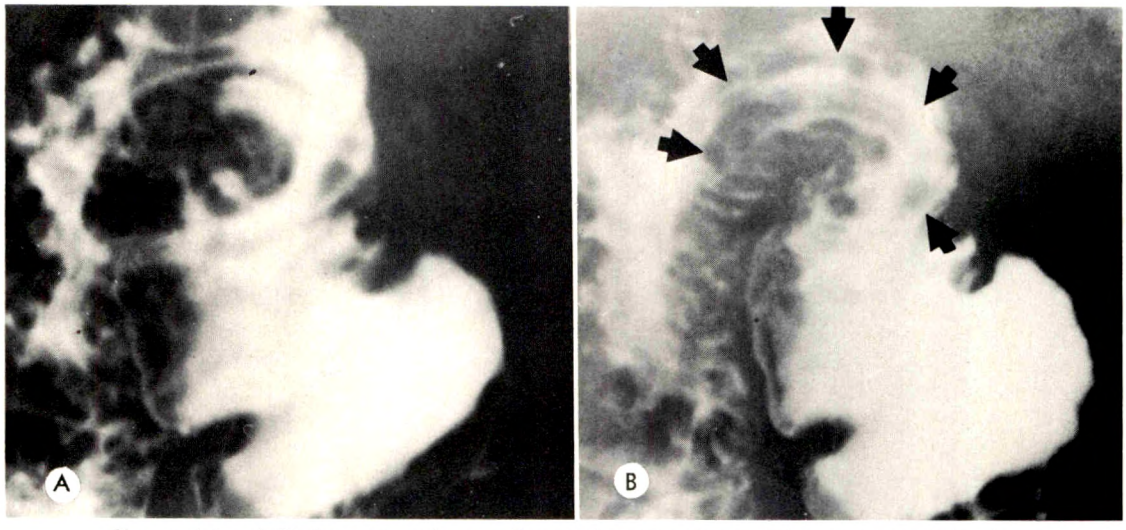


FIG. 2. (*A* and *B*) A contour abnormality at the same site with better mucosal detail. Surgery was not performed.

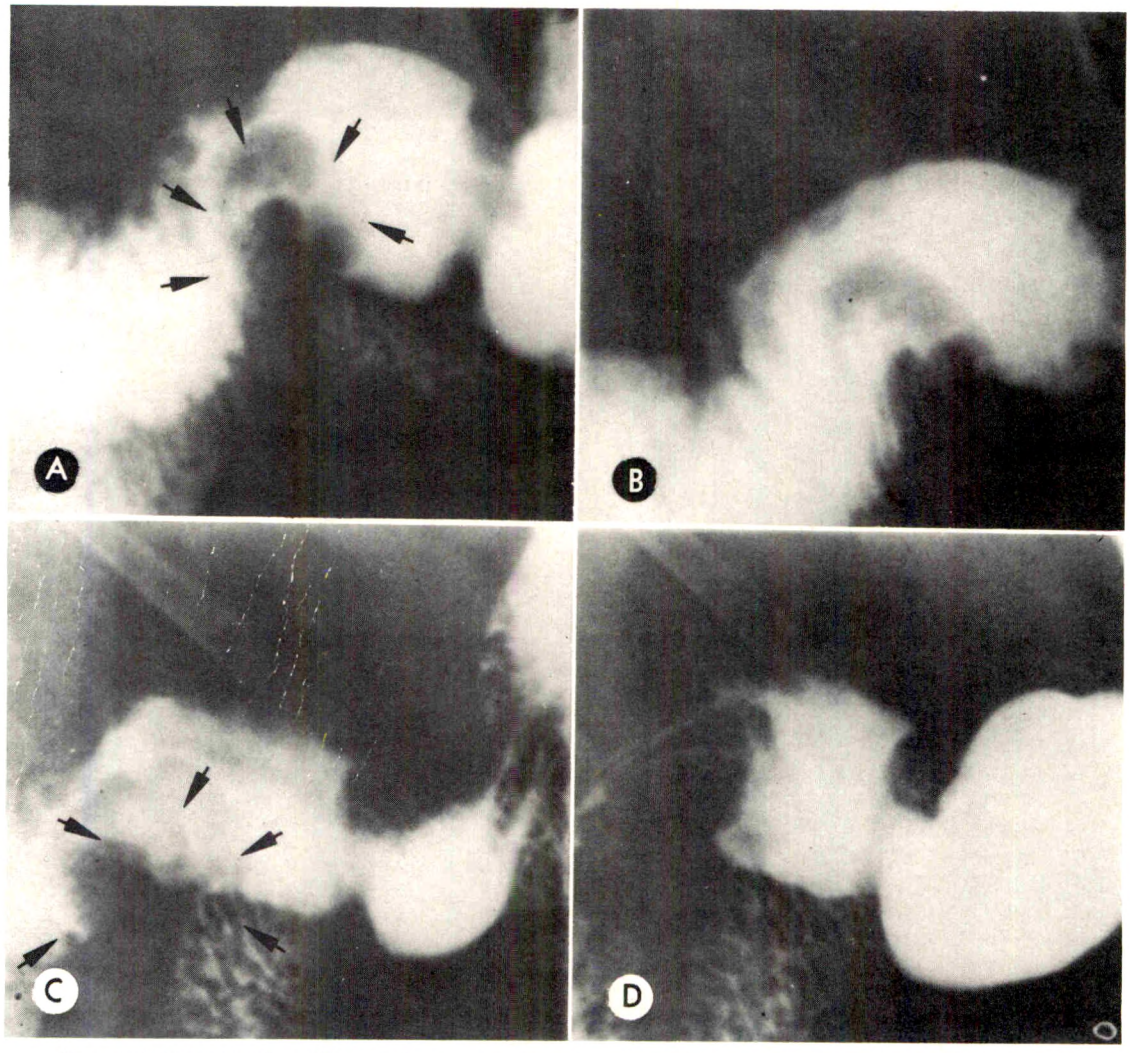
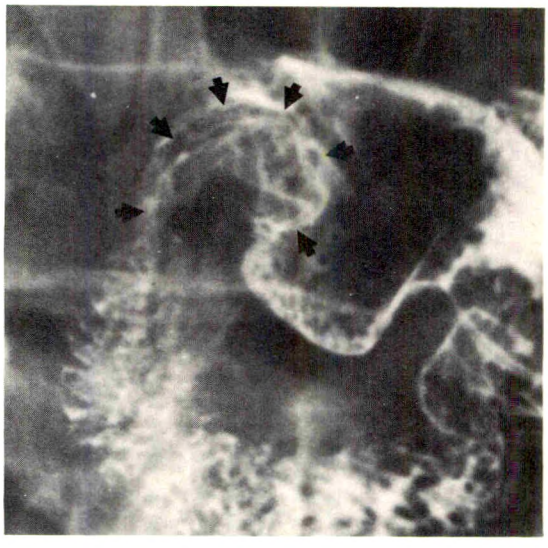


FIG. 3. (*A–D*) Another filling defect at the same location, with a more multilobular appearance. Endoscopy showed a prominent fold in the proximal duodenum.



reported by Kirby.[2] His study of the duodenal mucosa was obtained by making postmortem casts of the duodenum with radiopaque plaster. He noted the frequent occurrence of prominent normal folds in the region of the superior duodenal flexure. These casts have an identical roentgenographic appearance to the lesions seen in our patients.

Although many conditions may cause proximal duodenal polyps (Table 1),[1,3,5–8] the vast majority are benign. Much effort

FIG. 4. A similar filling defect, accentuated by the contraction of the descending duodenum.

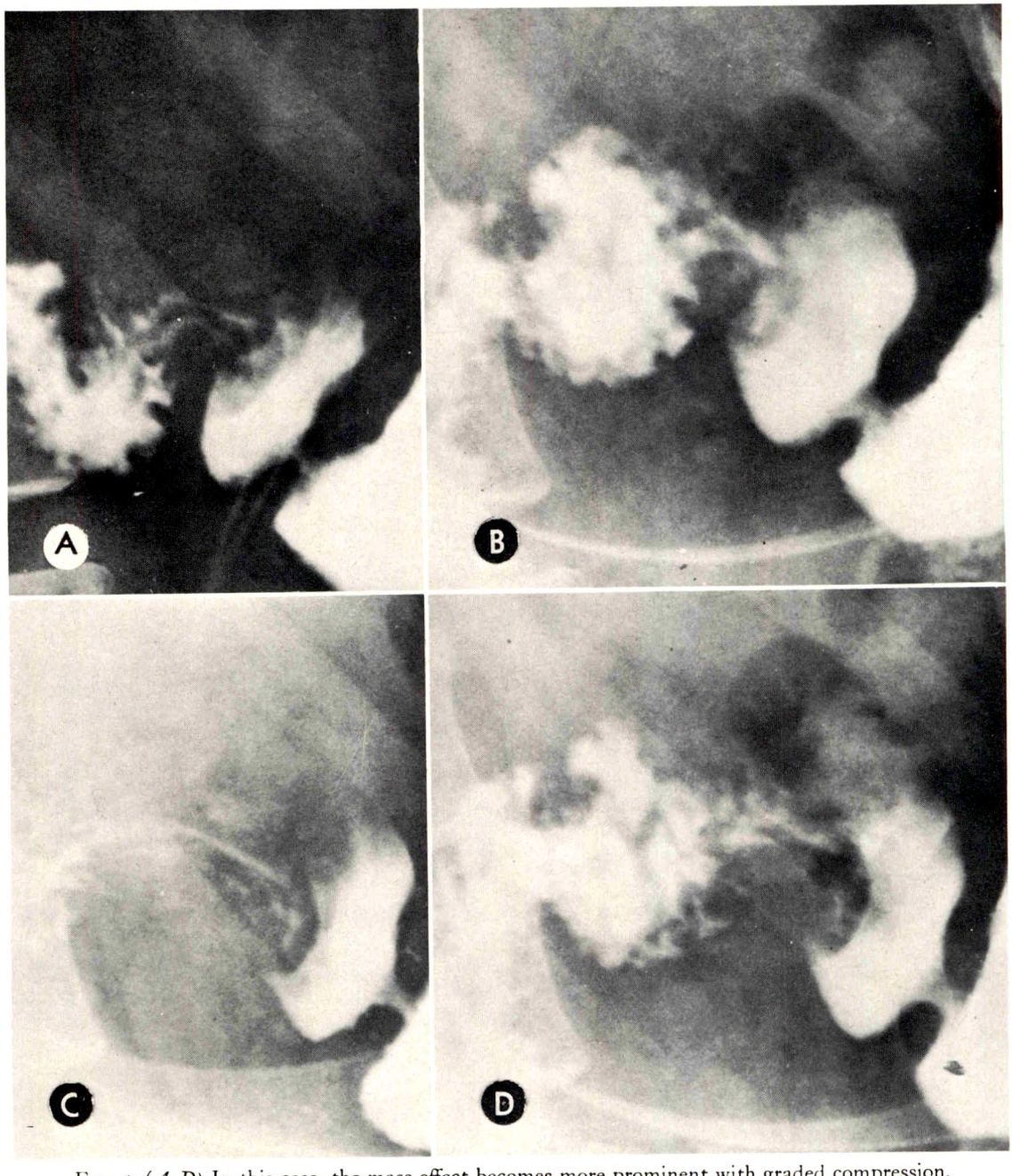


Fig. 5. (*A–D*) In this case, the mass effect becomes more prominent with graded compression.

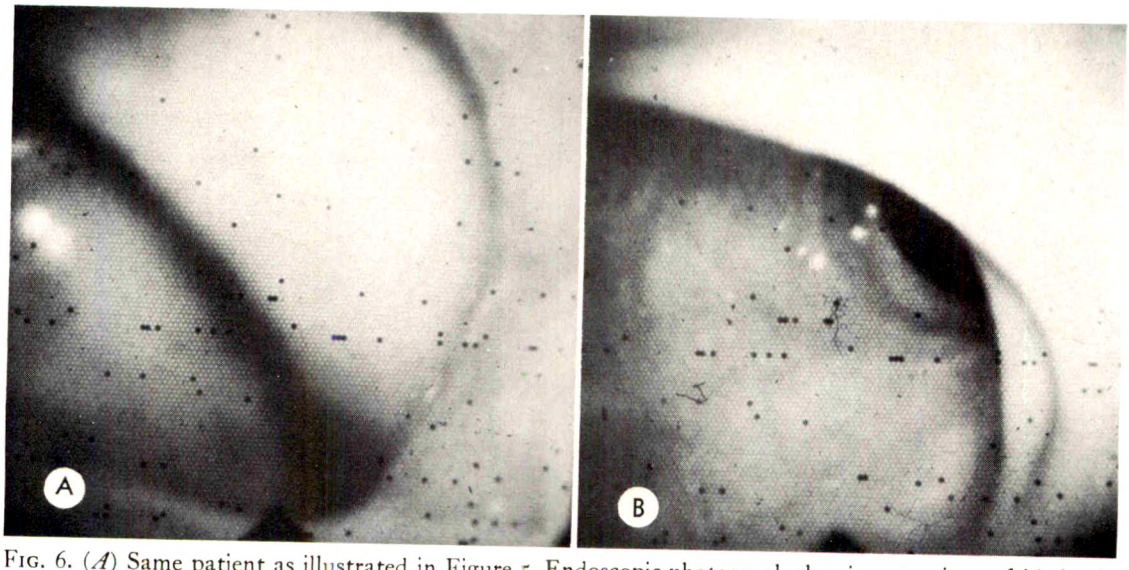


FIG. 6. (*A*) Same patient as illustrated in Figure 5. Endoscopic photograph showing prominent folds in the proximal duodenum without evidence of edema of ulceration. (*B*) Endoscopic photograph of the normal descending duodenum in the same patient.

and concern are expended to find the rare polypoid malignancies such as metastatic tumor or carcinoid. Since these malignancies are often submucosal, duodenoscopic biopsy cannot give diagnostic histologic material, and exploration and biopsy are required.

TABLE I

DIFFERENTIAL DIAGNOSIS OF DUODENAL POLYPOID MASSES

A. *Benign*	
	Adenomatous polyps
	Edema around small ulcer crater
	Gastric mucosal prolapse
	Varices
	Hypertrophy of Brunner's glands
	Intraluminal diverticula
	Angioma
	Lipoma
	Myoma
	Neurinoma
	Partial congenital bands
	Blood clot
	Mucosal deformity in acute or chronic pancreatitis
	Ectopic pancreas
B. *Malignant*	
	Metastatic nodule
	Carcinoid

Despite the fact that only 2 of our cases have full thickness duodenal biopsy proof confirmation, we believe that the entity described and illustrated here is characteristic of redundant duodenal mucosal folds accentuated by the flexure, and that biopsy is unwarranted. It should be interpreted as a normal variant.

SUMMARY

A roentgenographic finding caused by prominent mucosal folds in the superior duodenal flexure is described and illustrated.

Radiologists should become aware of this change, because it is so characteristic in location and appearance that further, more aggressive diagnostic work-up seems unwarranted.

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THE ROENTGENOGRAPHIC AND CLINICAL FINDINGS IN WHIPPLE'S DISEASE*

A REVIEW OF 8 PATIENTS

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WHIPPLE'S disease is an uncommon cause of malabsorption that is curable with antibiotic therapy. Previous articles on the roentgenographic features of Whipple's disease have described the small bowel features only subjectively. We wish to describe the clinical and roentgenographic findings in 8 patients, with an attempt at quantitating the roentgenographic appearance of the small bowel.

MATERIAL

Since 1963, 10 patients with Whipple's disease have been seen at the Mayo Clinic. Of these, the small bowel roentgenograms of 8 were available for study. The other 2 patients were excluded from the study, because their roentgenograms were not available, but these had been reported as showing a "malabsorption pattern." Six of the 8 patients were men and 2 were women; this distribution agrees with previous reports of male predominance.[11] The ages of the patients at diagnosis ranged from 34 to 66 years, with a mean of 53 years. The youngest patient in our series was a female.

RESULTS

ROENTGENOGRAPHIC FEATURES OF SMALL BOWEL (Table 1)

Previous papers have described coarse duodenal and jejunal folds in Whipple's disease in almost all cases, with little or no dilatation of the small bowel.[4,12,16,20] Of the 8 patients in our series, 7 had abnormal roentgenograms with coarse folds and slight dilatation of the small bowel. The small bowel was considered normal if

TABLE I

ROENTGENOGRAPHIC FINDINGS IN SMALL BOWEL OF PATIENTS WITH WHIPPLE'S DISEASE

Case	Roentgen Examination	Duodenum (mm.)		Jejunum (mm.)		Flocculation	Barium Dilution	Roentgen Findings
		Width	Fold Thickness	Width	Fold Thickness			
1	1st	27	3.0	30	3.5	None	Absent	Abnormal
2	1st	20	2.5	32	3.0	Grade 1	Present	Abnormal
	2nd (11 mo. later)	20	2.0	23	1.5	None	Absent	Normal
3	1st	30	2.5	36	3.5	Grade 1	Absent	Abnormal
	2nd (36 mo. later)	27	2.0	23	2.0	None	Absent	Normal
	3rd (62 mo. later)	25	2.0	24	2.0	None	Absent	Normal
4	1st	23	2.5	30	3.0	None	Present	Abnormal
5	1st	23	3.5	28	4.0	Grade 2	Present	Abnormal
	2nd (13 mo. later)	20	3.0	24	2.0	None	Absent	Normal
	3rd (25 mo. later)	18	2.0	24	2.0	None	Absent	Normal
6	1st	23	2.5	32	3.0	None	Absent	Abnormal
7	1st	23	2.5	25	2.0	None	Absent	Normal
8	1st	24	3.5	35	3.0	Grade 2	Present	Abnormal
	2nd (4 mo. later)	22	2.5	27	2.5	Grade 1	Absent	Abnormal (improved)

* From the Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

bowel wall, together with areas of ulceration in the later stages.[6] Lymphoid hyperplasia gives a nodular appearance rather than one of thickened folds.[8] The Zollinger-Ellison syndrome usually can be differentiated from Whipple's disease because there is ulceration and increased secretions, more severe in the duodenum than in the jejunum.[13] Intestinal lymphangiectasia is associated with a large amount of secretions within the small bowel.[14]

However, the positive identification of Whipple's disease is probably not possible roentgenographically, and small bowel biopsy is necessary to confirm its presence.

DISCUSSION

Because Whipple's disease is rare, large series of patients are difficult to find. The largest previous single series for whom roentgenograms were available involved 12 patients.[11] Of the 8 patients in our series, 7 had abnormal findings on small bowel roentgenograms, as judged both subjectively and objectively. This is the first time that such a quantitative assessment of the roentgenographic changes in Whipple's disease has been attempted, all other papers having confined the description of the small intestine to subjective description of thickening of mucosal folds, with only slight dilatation of the bowel.[4,12,16,20] In the patients in our series, measurement of the folds and jejunal and duodenal width confirmed these subjective impressions objectively; a dramatic decrease in these parameters was seen in the 4 patients who had roentgenographic studies repeated after treatment. As noted by Maizel *et al.*,[11] in their review of the literature, only 7 of 53 patients had normal findings on small bowel roentgenograms, and 4 of the 7 were in their second and third decades of life. In our series, the only patient with normal small bowel roentgenograms was a 34 year old woman.

The roentgenographic appearance in Whipple's disease is due to the infiltration of the mucosa and submucosa of the small bowel by PAS-positive macrophages, together with some lymphatic obstruction, resulting in widening of the villi and the valvulae conniventes. After treatment, these folds decrease in size.[7]

The present study also emphasized that

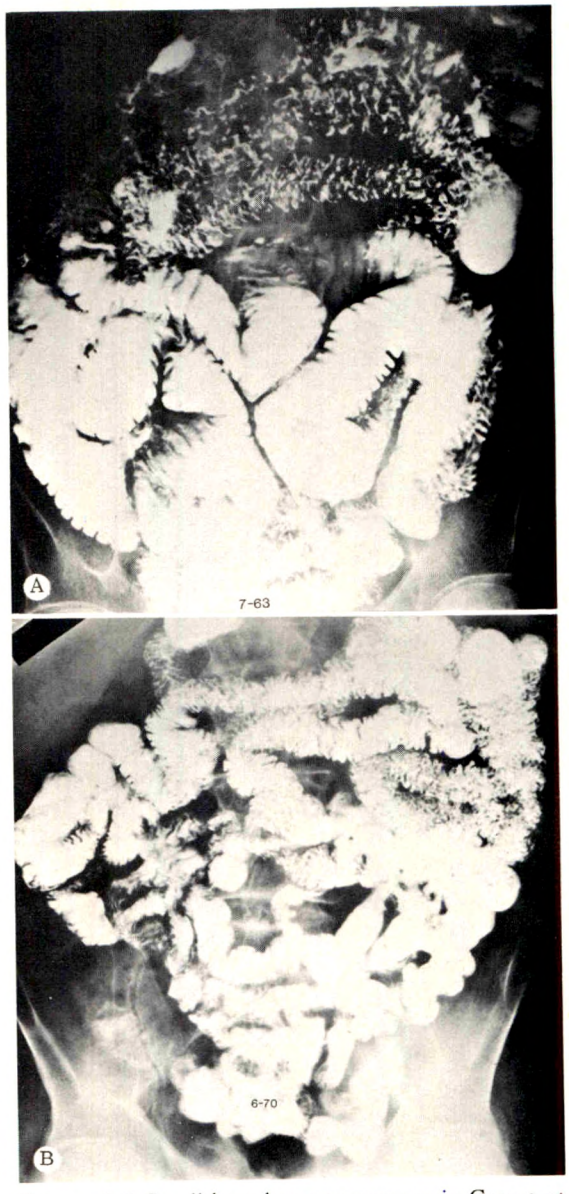

FIG. 2. (*A*) Small bowel roentgenogram in Case 2 at first visit showing thickened jejunal folds and some dilatation of jejunum. (*B*) Repeat examination 7 years later shows no abnormality. Jejunal biopsy specimen taken at this stage also showed no abnormality. Patient had taken tetracycline for 1 year.

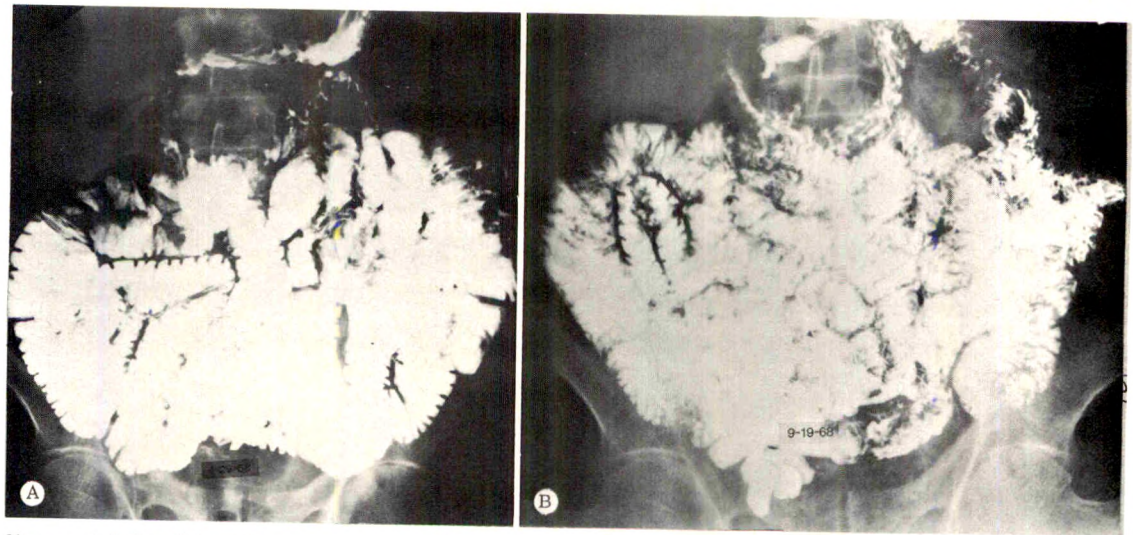

FIG. 3. (*A*) Small bowel roentgenogram in Case 8 at first visit showing dilated jejunum and thickened folds. Some dilution and flocculation of the barium are seen. Patient was weak and emaciated at time of this examination. (*B*) After 5 months of therapy, repeat examination shows evidence of improvement, but there is still slight dilatation of jejunum and thickening of folds. At this time, the patient felt well.

the roentgenographic signs in the small bowel in Whipple's disease are nonspecific. In most of our cases, the original report mentioned "malabsorption syndrome" or "deficiency pattern." However, the radiologist, when he is aware of this condition, can suggest the possibility of Whipple's disease if there is coarsening of the jejunal folds with little dilatation. All patients with a malabsorption pattern on small bowel roentgenograms should have a biopsy of the small intestine for definitive diagnosis.[18] The importance of making the diagnosis is emphasized by the fact that all 8 patients in our series showed marked improvement after treatment with tetracycline.

SUMMARY

Of 8 patients with Whipple's disease, 7 had roentgenographic findings consisting of slight dilatation of the small bowel, with thickening of the mucosal folds. The eighth patient had no abnormality on roentgenographic study.

This series represents the first in which the roentgenographic changes have been quantitatively assessed.

Confirmation of the diagnosis by biopsy is important because antibiotic treatment results in marked improvement both clinically and roentgenographically.

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THE ROENTGENOLOGIC SPECTRUM OF SMALL INTESTINAL CARCINOID TUMORS

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CARCINOID tumors are the most common primary neoplasms of the small intestine. Frequently, carcinoid tumors are small, asymptomatic, and discovered incidentally at surgery or necropsy.[12] Even when symptomatic, they may elude detection and create diagnostic difficulties due to the variety, subtlety, and non-specificity of both the clinical and roentgenologic manifestations. In one series, the delay in diagnosis averaged 4 years following the onset of symptoms with the roentgenologic diagnosis suggested in only 1 of 16 patients undergoing barium studies.[12]

Carcinoid tumors have stimulated considerable interest because of their potential pharmacologic activity and the associated clinical syndrome.[3,7] Relatively little emphasis has been given to the roentgenologic manifestations, although the radiologist will often have the first opportunity to establish the diagnosis.[1,6]

This communication presents our experience with 18 small intestinal carcinoid tumors. The spectrum of roentgenologic appearances is presented and correlated with the natural history of tumor growth.

MATERIAL

Medical records of all patients with histologically proven carcinoid tumors of the small bowel seen at the M. D. Anderson Hospital and Tumor Institute during the past 20 years were reviewed. Small intestinal barium examinations of diagnostic quality were available for study in 18 cases. Of these patients, 10 were males and 8 were females, ranging in age from 40 to 69 years. The primary neoplasm arose in the ileum in 17 cases and in the jejunum in 1 case.

The most common clinical symptom was crampy abdominal pain, which was usually associated with some degree of intestinal obstruction during the course of the disease. Four of the patients were considered clinically and by laboratory findings to have the carcinoid syndrome.

ROENTGENOLOGIC APPEARANCE

This series of small intestinal carcinoid tumors demonstrates a variety of roentgenologic appearances directly reflecting the mode of spread and extent of the disease. The appearances varied from a solitary intramural nodule to extensive mesenteric fibrosis where the primary neoplasm itself could not be identified. In most cases, considerable overlapping of the roentgenologic findings was present.

Although carcinoid tumors are believed to arise from cells deep in the mucosa,[9] roentgenologically they appear to originate in the submucosa. Three of our cases presented with smooth, solitary, intramural filling defects in the distal ileum (Fig. 1). With continued growth, the tumor may extend in a predominantly intraluminal direction with eventual obstruction. Similarly, the mass may serve as the lead point of an intussusception and cause obstruction in this manner. Differential diagnostic considerations of the solitary intramural carcinoid tumor include any benign tumor arising from mucosal or submucosal elements, aberrant gastric mucosa, or a solitary metastatic deposit.

Multiple nodules may result when the original lesion metastasizes to other parts of the bowel, or may be due to separately arising primary tumors. Multiple carcinoid

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tumors of the small intestine occur in approximately one-third of the cases with literally dozens of nodules of varying sizes being present.[12,14] Two of our cases vividly demonstrate multiple carcinoid tumors throughout the small bowel (Fig. 2, *A* and *B*). Similar roentgenographic appearances may be seen with lymphoma, diffuse metastatic disease of other origin, the Peutz-Jeghers syndrome, and neurofibromatosis.

As a carcinoid tumor enlarges, the intraluminal component is frequently exceeded by submucosal extension and outward growth through the bowel wall. An important and unique pathologic characteristic is the hypertrophic response of the muscular layers which develops as penetration of the wall occurs.[16] This results in thickening of the mucosal fold pattern and may contribute not only to narrowing of the bowel lumen, but also to separation of adjacent bowel loops (Fig. 3). The tumor may be predominantly extraluminal with minimal or absent intraluminal and intramural components. In such instances, the appearance may strongly suggest a purely extrinsic mass with compression and stretching of the adjacent bowel.

If a carcinoid tumor continues to extend exoenterically, it eventually involves the mesentery and tends to incite a pharmacologically mediated fibroplastic response.[5] Some manifestations of mesenteric desmoplasia were the most frequent and striking roentgenologic findings in our series, being present in at least 13 patients. In several instances, only findings related to the fibro-

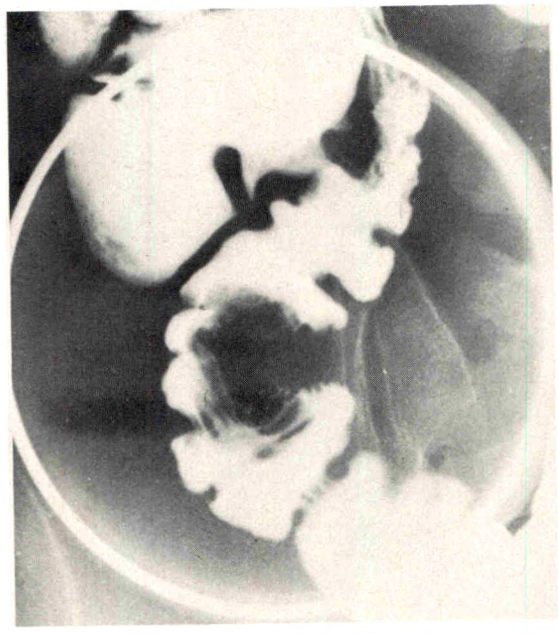

Fig. 1. Spot film of the terminal ileum demonstrating a solitary submucosal carcinoid tumor with a large intraluminal component.

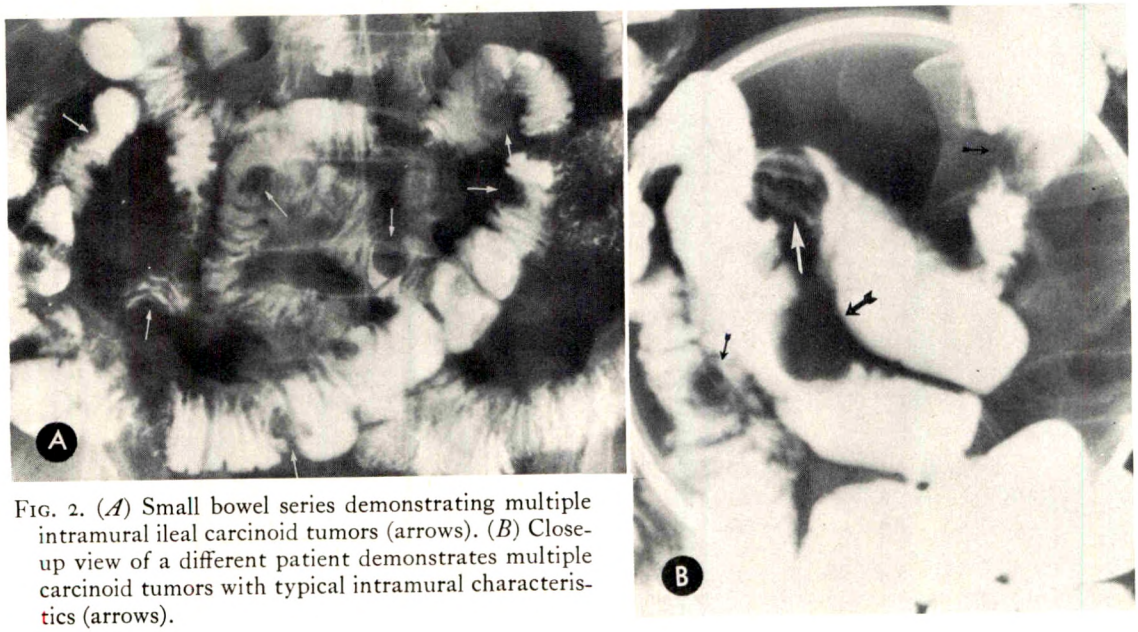

Fig. 2. (*A*) Small bowel series demonstrating multiple intramural ileal carcinoid tumors (arrows). (*B*) Close-up view of a different patient demonstrates multiple carcinoid tumors with typical intramural characteristics (arrows).

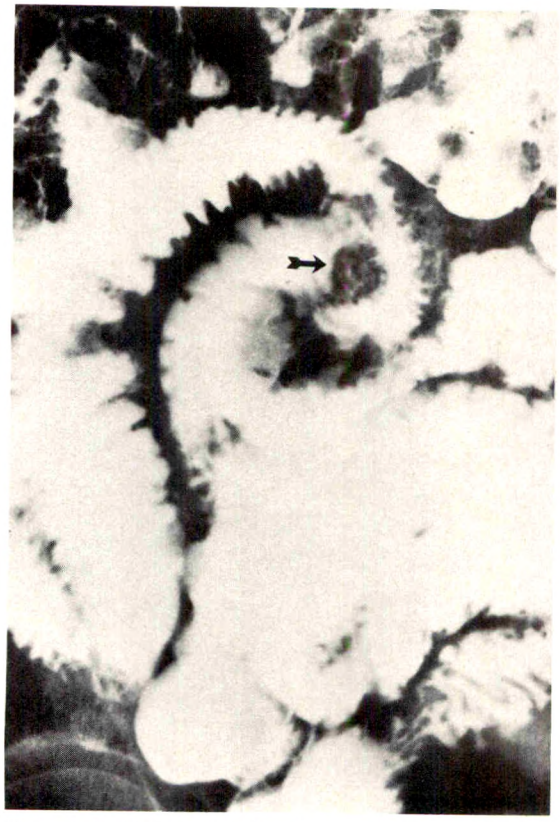

FIG. 3. Small bowel series demonstrating at least 1 carcinoid tumor (black arrow). There is associated thickening of the mucosal fold pattern and bowel wall due to a hypertrophic muscular response incited by the tumor.

plastic reaction were present with no actual tumor mass identifiable (Fig. 4). Mesenteric desmoplasia may have a variety of roentgenologic manifestations. At fluoroscopy, rigidity and fixation of bowel loops are noted despite vigorous palpation. If retraction toward the root of the mesentery is marked, a dramatic appearance of bowel loops arranged in a stellate or spoke-like fashion may be present (Fig. 5). Sharp angulation and kinking of one or more bowel loops were common and accounted for obstructive phenomena in the majority of our cases (Fig. 6). The desmoplastic reaction may also cause traction effects on the bowel wall. This results in an asymmetric transverse elongation of the barium-filled troughs between the mucosal folds (Fig. 7). These traction changes may be widespread but usually are localized. Extensive mesenteric fibrosis encasing the bowel, along with hypertrophic muscular thickening, may contribute to diffuse luminal narrowing (Fig. 4). One of our cases demonstrated thickening of the fold pattern throughout much of the small bowel, which may have been related to superior mesenteric venous occlusion by the fibrotic reaction. Total arterial obstruction resulting from mesenteric fibrosis may cause small bowel infarction, but this was not observed in our material. The roentgenographic changes occurring in carcinoid-induced desmoplasia are not specific and may be seen in a number of diseases that have significant mesenteric involvement. Abdominal carcinomatosis may produce similar findings, as may a variety of inflammatory processes such as postoperative adhesions, radiation enteritis, and granulomatous enteritis.

Although the roentgenologic appearance of carcinoid tumor may be most conve-

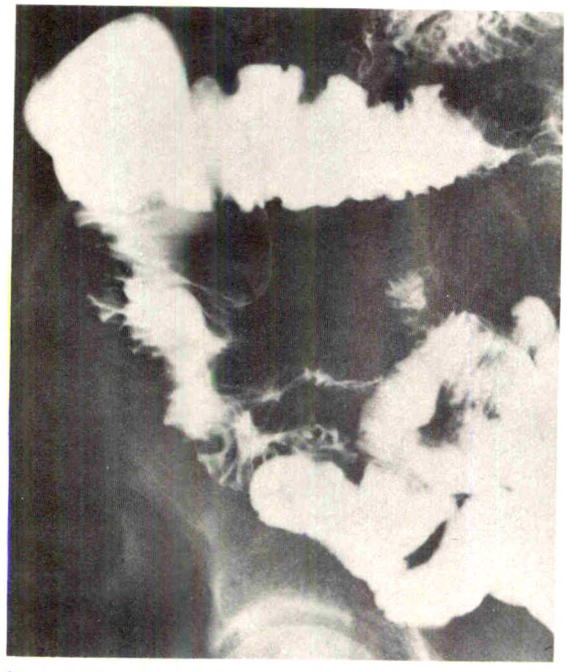

FIG. 4. Small bowel series demonstrating marked narrowing of the terminal ileum and associated traction changes of the cecum. The appearance is secondary to extensive tissue reaction, and actual tumor mass cannot be identified. The appearance resembles regional ileitis.

niently discussed if each stage of the disease is considered separately, most often several stages, each with its corresponding roentgenologic features, co-exist. Commonly, both tumor mass and fibroplasia are present (Fig. 8).

DISCUSSION

There are no histologic criteria which clearly differentiate between benign and malignant carcinoid tumors. In general, all small intestinal carcinoid tumors are considered to have malignant potential. The pathologic diagnosis of malignancy is based primarily on the degree of invasiveness and evidence of metastases, rather than cellular morphology.[9,18]

The majority of small intestinal carcinoid tumors are asymptomatic and discovered incidentally. In our series and in others, the most frequent presenting symptom was abdominal pain, often in association with partial or complete obstruction.[18] Despite a large body of literature about the carcinoid syndrome, it occurs in a relatively small percentage of symptomatic small bowel carcinoid tumors.[3] The more common components of the syndrome include diarrhea, wheezing, and cutaneous flushing. The syndrome is thought to be humorally-mediated, and, in the past, has been linked primarily to serotonin production by the tumor.[12] More recently, kallikrein, catecholamines, histamine, and prostaglandins have also been implicated.[11,13] When the carcinoid syndrome is present, there are virtually always concomitant liver metastases, since the tumor in the liver can excrete the hormonal products directly into the systemic circulation with avoidance of hepatic detoxification.[18]

The spectrum of roentgenologic features secondary to carcinoid tumors is more diverse than with most gastrointestinal neoplasms, primarily because of the variety of growth patterns and the tissue reactions incited by this disease. For this reason, carcinoid tumors should be considered in the differential diagnosis of both inflammatory and neoplastic small bowel lesions. In

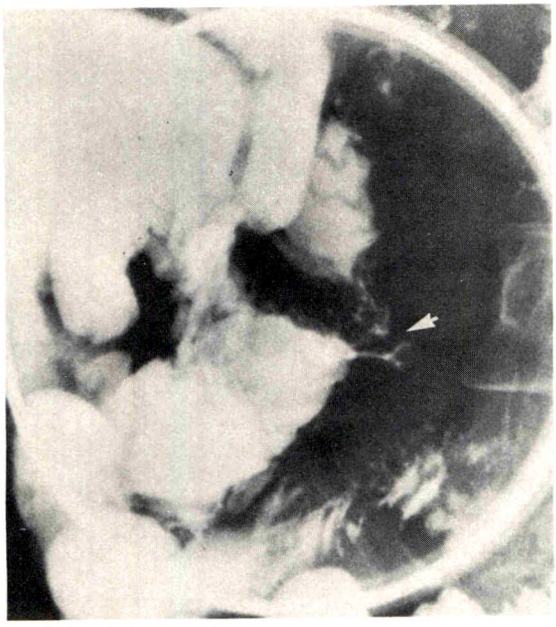

Fig. 6. Sharp angulation and narrowing of the distal ileum (arrow) resulting in moderate small bowel obstruction.

Fig. 5. Small intestinal examination showing a stellate configuration of a number of mid-ileal loops secondary to considerable mesenteric retraction. Several of the loops contain carcinoid nodules (arrows).

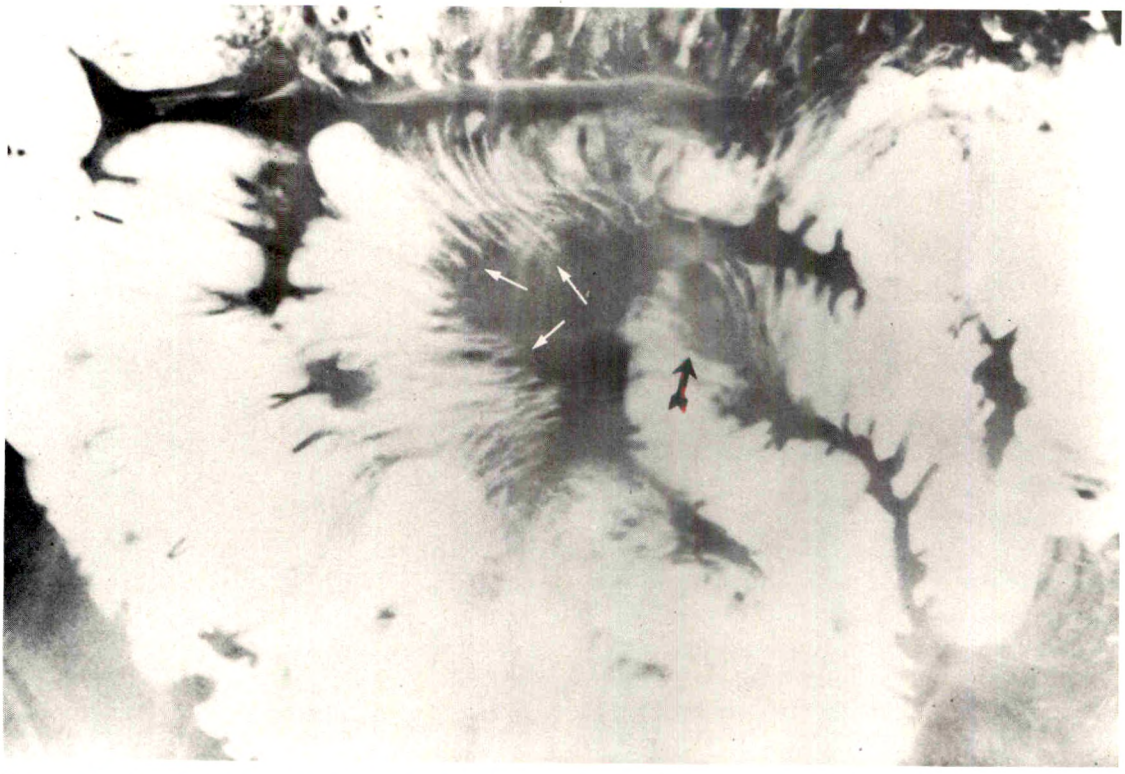

FIG. 7. Carcinoid tumor demonstrating prominent traction changes on a mid-ileal loop of bowel (white arrows). There is separation of adjacent bowel loops and at least 1 intramural nodule is present (black arrow).

particular, when there is evidence of solitary or multiple submucosal nodules and/or when manifestations of mesenteric disease are present, carcinoid tumor is a likely diagnosis. Obstruction is the most common complication, usually occurring in association with the desmoplastic mesenteric reaction. Less frequently, it may result from local tumor growth or intussusception. Although frank ulceration associated with carcinoid tumor has been documented,[8] it was not present in any of our cases.

Visceral angiography may be helpful in the evaluation of a suspected carcinoid tumor when clinical and laboratory findings are suggestive but the barium study is normal. If the barium examination is abnormal, angiography can aid in the differentiation of carcinoid tumor from other neoplastic processes. When the diagnosis has been established, a vascular study will determine the presence of liver metastases. Angiographically, carcinoid tumors have a somewhat characteristic appearance, which is also a manifestation of the desmoplastic reaction. The most common features are kinking, irregularity, or obstruction of distal intramesenteric arteries. Usually the mesenteric veins are also totally obstructed.[2,15] In most cases, there is no significant neovascularity or tumor stain, although the injection of epinephrine can dramatically accentuate the tumor stain of both the primary lesion and hepatic metastases.[4]

Careful small intestinal examination is essential, since a barium study often provides the first and perhaps only opportunity short of laparotomy to suggest the diagnosis. Moreover, prognosis appears to be directly correlated with the tumor size and resectability, even if complete bowel wall and mesenteric invasion have oc-

curred.[12,18] In addition, preoperative consideration of the diagnosis is important for safe anesthesia in patients with elevated vasoactive hormonal levels.[10]

SUMMARY

The roentgenologic features of small intestinal carcinoid tumors have received little attention in the literature compared to their clinical and potential pharmacologic manifestations. Eighteen proven cases were analyzed.

A variety of roentgenologic appearances may be present, reflecting the growth patterns and tissue reaction incited by the tumor. Roentgenologic appearances vary from solitary or multiple submucosal nodules to extensive mesenteric desmoplasia without demonstration of a tumor mass. Some manifestation of the desmoplastic reaction is the most common roentgen finding.

Because of the nonspecific clinical findings, the radiologist will often have the first opportunity to suggest the diagnosis.

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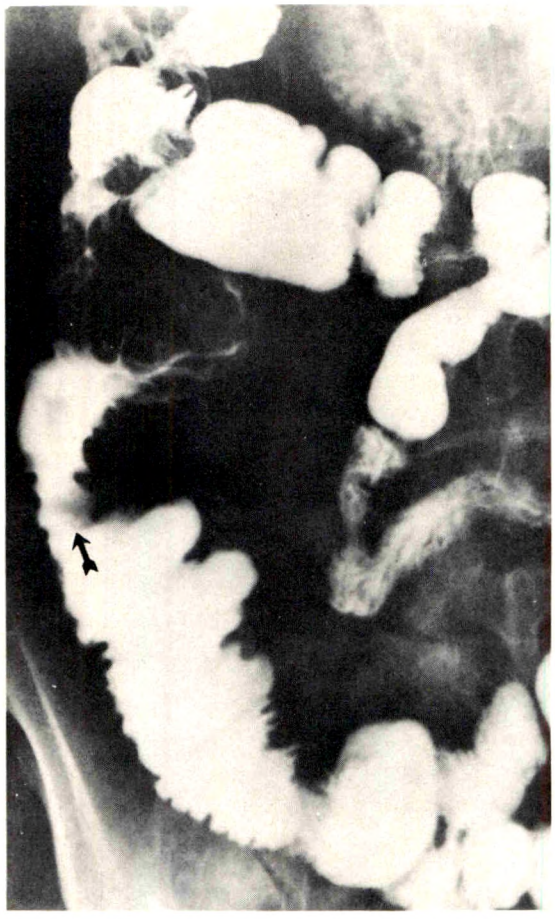

Fig. 8. Carcinoid tumor of the distal ileal area demonstrating a number of features. A tumor mass is identified which has both intraluminal (black arrow) and extraluminal components. There is persistent encasement of the distal ileum. Considerable mesenteric reaction is present separating the bowel loops and causing angulation of an adjacent distal ileal loop.

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Vol. 123, No. 2

DIASTATIC RUPTURE OF THE CECUM IN OBSTRUCTING CARCINOMA OF THE LEFT COLON

RADIOGRAPHIC DIAGNOSIS AND SURGICAL IMPLICATIONS

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THE cecum may rupture as a result of a mechanical obstruction of the distal large bowel. This has been termed a diastatic rupture in reference to the mechanism of injury. It is thought that the distention of the cecal wall leads to a separation of the muscular layers through which the mucosa protrudes and ultimately ruptures at the site of this protrusion. The most common cause for the distal obstruction with cecal perforation is carcinoma of the colon.[2,6,7] This results in a characteristic radiologic triad of a massive pneumoperitoneum, a gastrointestinal air pattern indicative of a distal obstruction of the large bowel and marked dilatation of the cecum. It is curious and seemingly contradictory that the cecum is dilated in the presence of a perforation.

Four cases of cecal perforation in association with distal colonic carcinomas are presented and an explanation for the etiology and pathomechanics of the diastatic rupture is offered. The surgical implications are discussed.

MATERIAL

Four patients with diastatic rupture of the cecum were encountered: 2 males and 2 females ranging in age from 55 to 82 years. All were found to have an obstructing carcinoma of the sigmoid colon. In 2 cases the perforation occurred prior to admission and in the other two after admission while under observation.

REPORT OF CASES

CASE I. This 78 year old male was seen in the emergency room complaining of constipation of two weeks' duration, associated with cramping abdominal pain for 1 week. Physical examination revealed a distended abdomen. There was marked tenderness to palpation.

Roentgenograms of the abdomen demonstrated a massive pneumoperitoneum. Both small and large bowel were distended. The transverse diameter of the cecum measured 11 cm. (Fig. 1, *A–C*).

A laparotomy was performed. The abdominal cavity contained a large amount of air and feces. Exploration revealed a carcinoma of the sigmoid colon. A resection of the right colon and a right transverse colostomy and ileostomy were performed.

Following surgery the patient's condition progressively deteriorated. He expired on the third postoperative day.

CASE II. This 82 year old male complained of abdominal pain of one week's duration. On admission the patient's abdomen was distended and diffusely tender to palpation.

Roentgenographic examination of the chest and abdomen demonstrated dilated loops of small and large bowel. The cecum was distended measuring 10.5 cm. in its transverse diameter. An extensive pneumoperitoneum was present (Fig. 2, *A* and *B*).

A laparotomy was performed which disclosed an obstructing carcinoma of the sigmoid colon. A tube cecostomy and transverse colostomy were performed. The patient's condition progressively deteriorated following surgery and he expired on the first postoperative day.

Comment. Cases I and II demonstrate the characteristic findings of massive pneumoperitoneum, obstruction of the large bowel and marked distention of the cecum. These 2 cases also demonstrate the poor prognosis that this combination of roentgenographic findings imply.

CASE III. This 55 year old female noted pro-

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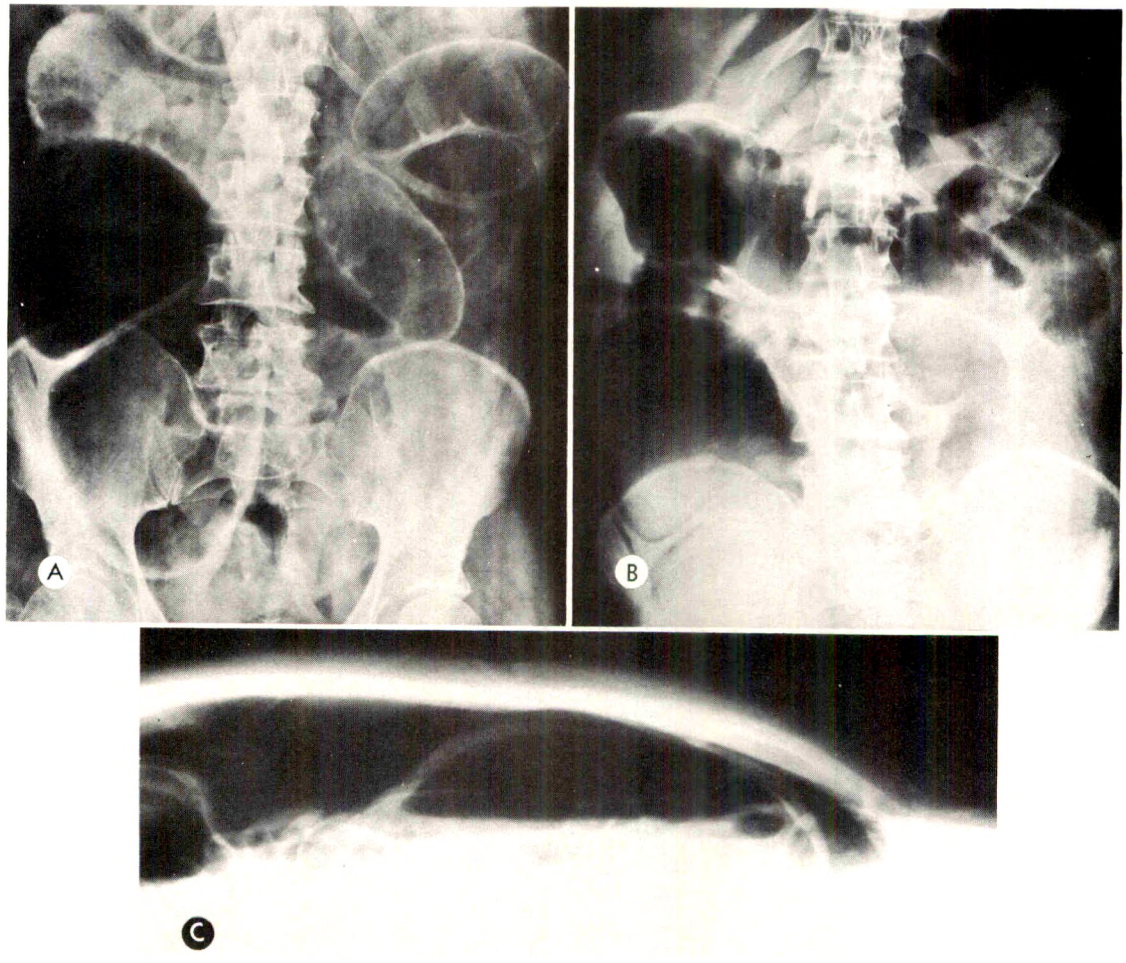

FIG. 1. (*A*) Pneumoperitoneum with distention of cecum measuring 11.0 cm. Dilated loops of bowel seen. (*B*) Pneumoperitoneum demonstrated with air on both sides of bowel wall. (*C*) Massive pneumoperitoneum demonstrated.

gressive constipation over a period of 6 months. Abdominal pain was first noted 2 weeks prior to admission. The pain gradually intensified and became associated with nausea and vomiting. The patient was admitted to a hospital. Physical examination revealed a pale dehydrated female with distended abdomen. A digital examination of the rectum revealed a hard, irregular mass within the rectum. Proctoscopic examination disclosed a fungating mass of the rectum almost completely occluding the rectal lumen. A biopsy was performed. Microscopic examination revealed adenocarcinoma. A chest roentgenogram demonstrated the presence of metastatic deposits within the lungs.

The abdominal distention was unchanged. The initial roentgenographic evaluation of the abdomen demonstrated a partial obstruction with suggestion of perforated viscus manifested by air on both sides of the bowel wall, the "double wall" sign. The cecum was dilated measuring 10.5 cm. (Fig. 3, *A* and *B*). She was observed for 4 days. On the fifth hospital day a laparotomy was performed and examination disclosed generalized peritonitis and an abscess in the left abdomen which was drained. The right side of the abdomen was not examined. A transverse colostomy was performed through a small incision in the mid-abdomen. Extensive peritoneal metastases were found. Postoperatively her condition remained stable for approximately 10 days. On the tenth postoperative day, as the cutaneous sutures were removed, the wound dehisced and fecal drainage appeared. A barium enema examination was then performed through the colostomy demon-

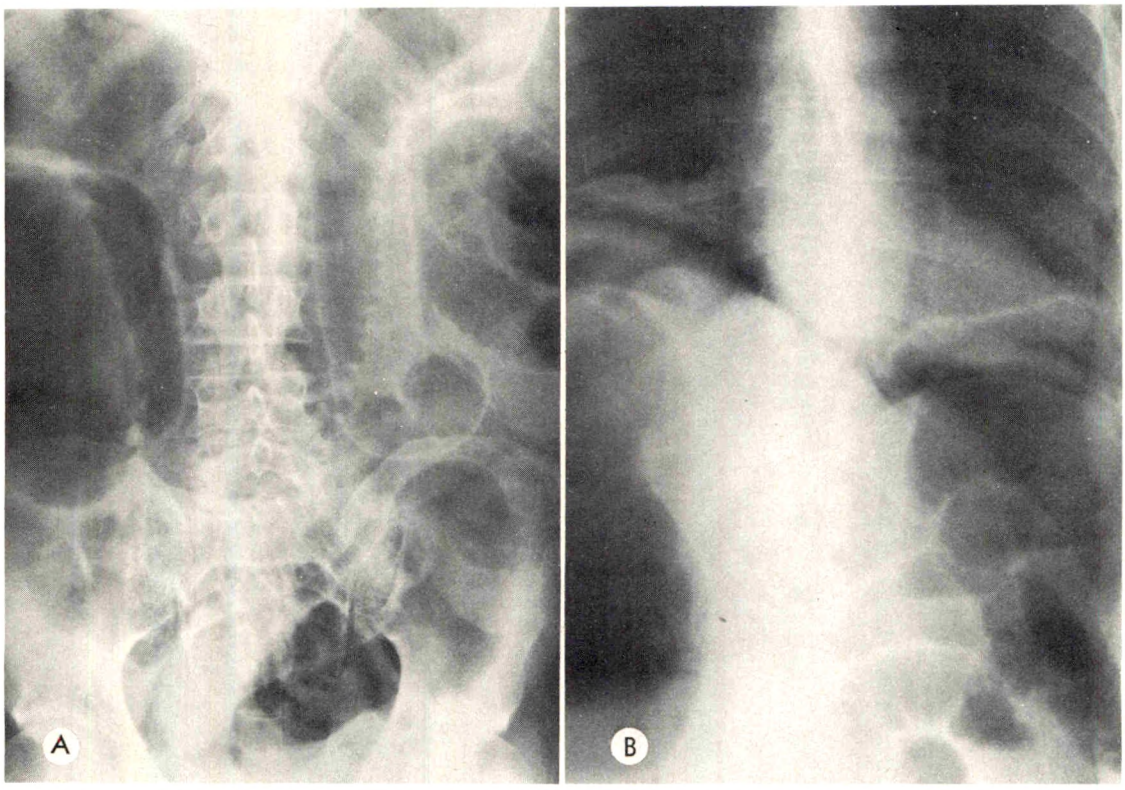

Fig. 2. (*A*) Dilated loops of bowel with distention of cecum measuring 10.5 cm. (*B*) Massive pneumoperitoneum demonstrated.

strating a perforation of the cecum (Fig. 3*C*). She progressively deteriorated and died on the twentieth postoperative day.

Comment. Case III demonstrated the necessity of examining the cecum at the time of surgery in the face of an obstructing carcinoma of the colon. This is the only method by which one can absolutely exclude the presence of an impending or existing rupture of the cecum under these circumstances.

Case IV. This 59 year old female was admitted with cramping abdominal pain, nausea and vomiting of ten days' duration. She had not had a bowel movement in one week. Physical examination demonstrated a tense, distended, tender abdomen.

Roentgenograms revealed dilated loops of small and large bowel with air fluid levels. The transverse diameter of the cecum measured 11 cm.

A barium enema examination demonstrated an obstructing annular carcinoma of the proximal sigmoid colon (Fig. 4).

A laparotomy was performed 3 days following the barium enema examination. Upon entering the peritoneal cavity a large amount of free air escaped and gross fecal spillage was obvious. An annular carcinoma of the sigmoid was identified. There was a rupture of the anterior wall of the cecum. The sigmoid carcinoma was resected and a double barrel colostomy was established. The patient progressively deteriorated postoperatively and died within 24 hours.

Comment. Case IV demonstrates the hazard of prolonged delays in the performance of surgical decompression of a dilated cecum in the face of a distal colonic obstruction.

DISCUSSION

PATHOMECHANICS

An obstruction of the intestinal tract produces distention of the bowel proximal to the point of obstruction. Given equal pressure throughout the colon, the greatest distention will occur in that portion of the colon with the largest diameter, the

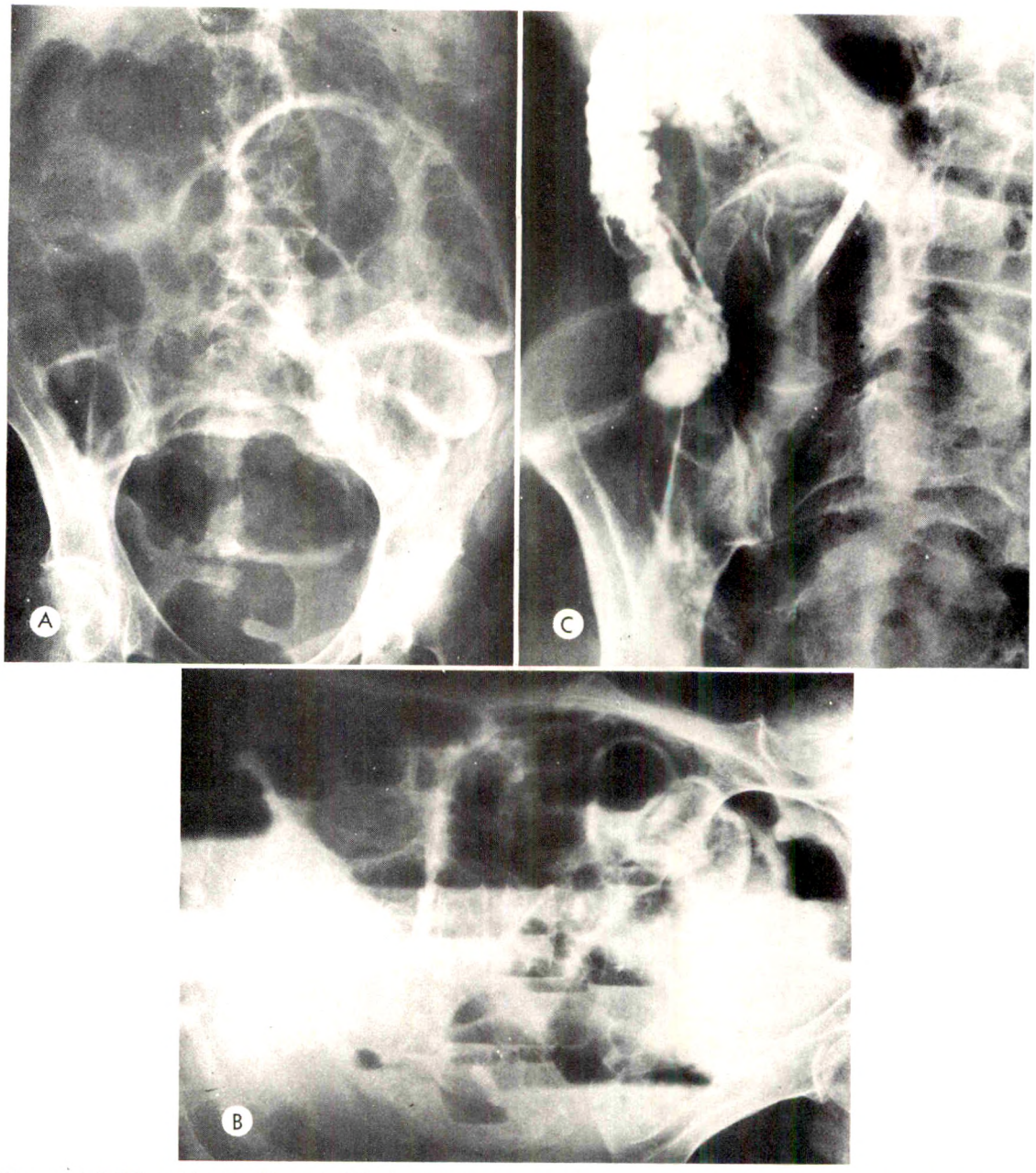

FIG. 3. (*A*) Dilated loops of bowel with distention of cecum. Air seen on both sides of bowel wall. (*B*) Dilated loops of bowel with air-fluid levels and air on both sides of bowel wall. (*C*) Barium enema examination through colostomy demonstrating perforation of the cecum with extravasation of barium.

cecum. This is explained by the Law of LaPlace[10] which states that the pressure required to distend the walls of a hollow viscus is inversely proportional to its radius, the greater the radius the less pressure required. This is mathematically stated in the formula $T=PD$ (where T equals wall tension, P equals intraluminal pressure, and D equals the diameter of the viscus). The tensile strength of the colon wall will be exceeded sooner in that portion of the colon that has the greatest diame-

ter.[10] The intraluminal pressure needed to produce perforation is between 20 and 55 mm. Hg.[3,7,9]

The resultant perforation is most commonly found on the anterior surface of the cecum. It may vary in length from 5 to 40 mm. with its longest diameter parallel to the longitudinal axis of the intestine.[8] The margins of the rupture are sharp and show no evidence of previous inflammation. The tear in the outer longitudinal muscle layer is wider than the tear in the inner circular muscle layer. There may be multiple tears in the same segment of a tear or tears through the entire wall may be seen in association with other areas, wherein the mucosa is seen to protrude through the diastasis of the muscle layers of the cecum as described above. Microscopically, atrophy of all layers with only a minimal degree of edema or round cell infiltration indicative of inflammation is seen. In almost all reported cases, no gross or microscopic evidence of pre-existing mucosal inflammation or ulceration could be seen in the distended or ruptured bowel.

Three theories have been proposed to explain the cecal perforation.[8] A vascular theory states that as the lumen of the intestine distends, the blood vessels within its walls become obliterated and the area supplied by these vessels becomes necrotic. A hemorrhagic infarction is thus produced which, in turn, is followed by perforation. Although the tear is usually situated on the anterior mesenteric border or the anterior wall of the cecum which has a poor blood supply, there would appear to be little, if any, microscopic evidence to support this theory. A toxic infectious theory has been proposed which states that there is an increase in the virulence of bacterial flora in the closed loop obstruction of the intestine and an increase in the permeability of the intestinal wall. This leads to bacterial invasion of the mucosa with subsequent necrosis, ulceration, and extension of the process to the outer layers of the wall with a resultant transmural perforation. Likewise there is little microscopic support for such a course of events. The mechanical theory then appears to best explain the perforation. Progressive distention of the cecum leads to a diastasis of the muscular wall through which the mucosa protrudes and ultimately ruptures.

Fig. 4. Dilated loops of bowel with distention of the cecum measuring 11.0 cm. Barium enema demonstrating obstruction in the sigmoid. (Courtesy of A. F. Barrett, M.D., Houston, Texas.)

Roentgenographic Findings

Roentgenograms of the abdomen in the presence of a ruptured cecum secondary to a distal colonic obstruction were first described by Rack.[7] He stated that the combination of large quantities of free intraperitoneal air in association with greatly distended loops of colon, especially the cecum, with or without distention of the small intestine would suggest the diagnosis.

It is curious and seemingly contradictory that following perforation and an accumulation of a large amount of free air in the peritoneum, the cecum would remain

greatly distended. A precise explanation as to why the cecum does not collapse or decompress under these circumstances is not available. It has been suggested that a perforation is sealed by the omentum or adjacent bowel,[7] but this is not supported by surgical or autopsy findings wherein an open perforation is identified. For the cecum to collapse, it might be presumed that the intraperitoneal pressure would have to exceed the intraluminal pressure of the colon. It may be that an equilibrium is achieved between the distended colon and peritoneal cavity and, therefore, the cecum remains distended.

SURGICAL IMPLICATIONS

Ruptures of the cecum in association with large bowel obstruction carry a very high degree of morbidity and mortality. The mortality ranges from 36 to 72 per cent.[1,5] In the face of a distal colonic obstruction, the cecum should be examined at the time of surgery for impending or actual perforation. Some authorities have stated that a cecostomy is preferable to a transverse colostomy in the presence of a distal bowel or large bowel obstruction.[4] While we are in no position to argue this point, it would seem wise to examine the cecum thoroughly before perforation of the cecum. This would obviate or prevent the oversight of such a perforation with its attendant morbidity and mortality as is demonstrated by Case III.

Some have attempted to relate the transverse diameter of the cecum to the possibility of impending cecal perforation. Davis and Lowman[5] stated that when the transverse diameter is over 9 cm. it should be suspected of impending perforation. The transverse diameter of the cecum in the present cases measured 11 cm., 10.5 cm., 10.5 cm., and 11 cm., respectively. In our experience, 9 cm. would seem to be a low figure since we have encountered numerous cases of cecal distention of this magnitude which did not result in perforation. There is some urgency in the performance of surgical decompression of a dilated cecum in the face of a distal colonic obstruction. Prolonged delays may allow the cecum to perforate with resultant peritonitis as is demonstrated in Cases III and IV.

SUMMARY

Four cases of diastatic rupture of the cecum in association with an obstructing carcinoma of the left colon are presented.

Abdominal roentgenograms demonstrating massive pneumoperitoneum, dilated cecum, and distal obstruction of the colon are considered characteristic of this entity.

At the time of surgery for obstructing carcinomas of the colon, the cecum should be inspected for diastatic perforations.

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ISCHEMIC COLITIS*

RADIOLOGY AND PATHOPHYSIOLOGY

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SPONTANEOUSLY occurring ischemic colitis, the result of acute deprivation of blood flow to a portion of the colon, has become a commonly recognized entity since Boley *et al.*[5] defined its clinical and radiographic characteristics and perfected an experimental animal model. Several excellent papers have described various radiologic aspects of the disease,[11,16,23] but none has defined the contributions of the different radiologic techniques in developing a firm diagnosis.

Our experience with 41 patients with ischemic colitis has provided not only a basis for evaluating the usefulness of different radiographic techniques, but has also substantiated our original observations[30] about the etiology and allowed the development of a simplified approach to this disease.

MATERIAL

Spontaneous ischemic colitis (SIC), as many inflammatory diseases of the colon, must be defined in clinical, radiologic and pathologic terms since none of these factors is specific when taken by itself. In order to permit evaluation of a "pure" group of spontaneously occurring ischemic colitis, the following criteria were used for inclusion in this group of patients: (1) an acute lower gastrointestinal problem occurring in a person over 50 years of age without a similar previous or subsequent episode; (2) the process occurs in a patient not being treated with antibiotics; without evidence of enteric infection, colonic obstruction, previous abdominal vascular surgery or collagen vascular disease; (3) proctoscopic observation, when positive, indicated an acute mucosal inflammatory disease; (4) radiologic findings, when positive, are those of a colonic ulcerative or exudative process which, in surviving nonoperated patients, undergoes evolution to complete healing or stricture; (5) there is no radiographic or pathologic evidence of ischemia elsewhere in the gastrointestinal tract; and (6) available histologic specimens demonstrate mucosal necrosis with submucosal edema and/or hemorrhage.[18] Noteworthy in this definition is that nowhere is *occlusive* vascular disease mentioned as a fundamental requirement of SIC. It is recognized that the use of these strict criteria may lead to exclusion of *bona fide* cases of SIC; they purposefully prevent inclusion of patients with the nonspontaneous forms of ischemic disease associated with other etiologies. As a result, patients with inflammatory colonic disease known to be associated with the following phenomena were excluded from our analysis: (1) colonic obstruction, (2) vasculitis, (3) hematologic disorders, (4) previous aortic or mesenteric vascular surgery, (5) systemic infections with enteric organisms, (6) previous history suggesting bowel symptoms attributable to either Crohn's disease or idiopathic ulcerative colitis; and (7) ischemic disease of the small bowel.

This retrospective analysis of 41 patients includes 6 of the 7 previously reported patients[30] who fulfilled the present criteria. Case III of that previous report has been

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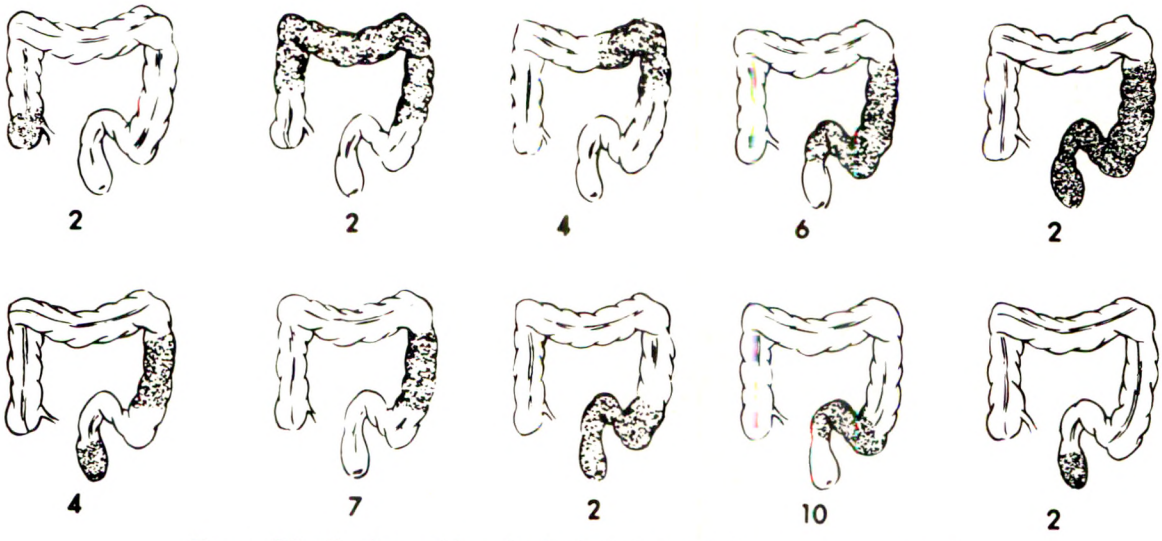

Fig. 1. Distribution and length of colonic ischemia in 41 patients. Note the infrequency (15 per cent) with which the splenic flexure is involved.

eliminated because of the previous history of intermittent diarrhea. Included in the present group are 21 men and 20 women, ranging in age from 55 to 89 (average, 70 years). The racial distribution includes 39 Caucasians, 1 Oriental and 1 American Indian. The absence of Negroes in this group is of interest, since all but 5 patients were treated in a hospital in which the ratio of Negro to Caucasian admissions is 2 to 3.

The major symptom of abdominal pain was present in 74 per cent and was usually mild and poorly localized to the lower abdomen; 67 per cent of the patients presented with diarrhea and in two-thirds of these, bright red blood was reported. The stool guaiac was positive in 92 per cent on admission. The most common admitting diagnosis was diverticulitis.

The duration of the ischemic process was considered to be that period from initial abdominal symptoms to admission. In 80 per cent of patients in whom this could be documented, the duration was less than 96 hours; in 3 patients it was 14, 15 and 21 days. The duration of symptoms and signs could not be correlated with the severity of the documented ischemic process.

Figure 1 shows the distribution of colonic lesions as determined by proctoscopic, radiologic and, when available, pathologic data. The distribution differs from a previous large series[4] in the higher incidence of involvement distal to the splenic flexure (80 per cent). Fifteen of the 41 patients required surgery and of these, 8 survived. Eighteen of the 26 patients treated conservatively survived. Surgical and/or autopsy specimens were available in 13 patients. In 17 patients, endoscopy revealed findings in the rectum and/or sigmoid colon consistent with ischemic colitis. That impression was confirmed in all 5 who had biopsies. In 11 patients, the basis of the diagnosis was clinical findings coupled with one or more barium enema examinations.

Plain Film Abdominal Roentgenography

Conventional supine and upright roentgenograms of the abdomen were initially obtained. If specific signs suggesting ischemia were detected, an immediate repeat supine film roentgenogram was obtained to determine the consistency of this observation. Angiographic scout films represented

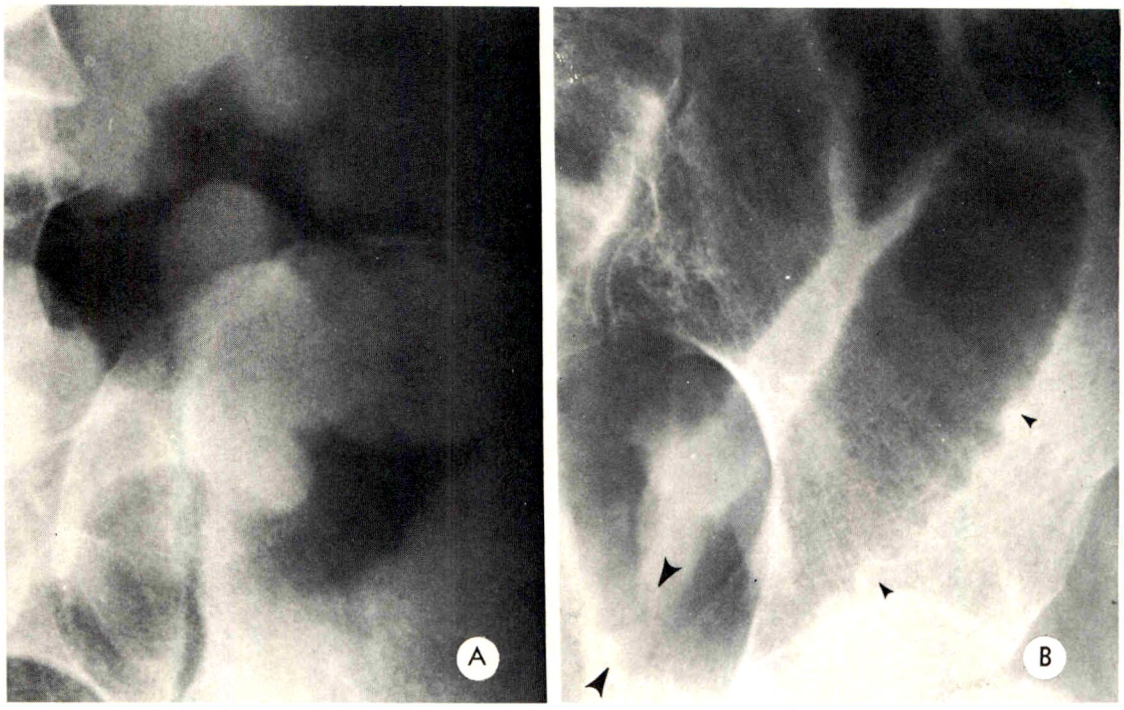

Fig. 2. (*A*) Multiple large soft tissue densities scattered throughout the sigmoid colon (see Figure 6 for angiogram on this patient). (*B*) Multiple tiny soft tissue densities (small black arrows) are present in the proximal sigmoid colon. Note also the loss of haustral markings and the rigid appearance, particularly at the flexure (large black arrows).

a further potential source of positive plain film findings.

Multiple, soft tissue, rounded densities outlined by intraluminal gas ("thumbprints") (Fig. 2, *A* and *B*) were considered necessary for a positive diagnosis. This finding must be interpreted with caution since its configuration may be closely mimicked by a normal colon in various degrees of incomplete distention. Therefore, a positive diagnosis was made only if these observations were present in a distended colon or were accompanied by other abnormal signs, the most common being rigidity of the bowel wall. A single patient presented with free abdominal gas, but we encountered none of the other rare complications of ischemia such as intramural gas,[24] portal vein gas,[28] or megacolon.[22] Positive signs warranting a presumptive diagnosis of ischemic colitis were present in 21 per cent of the patients. These could not be correlated with the duration of symptoms or prognosis. In an additional 18 per cent findings of rigidity and tubulation (lack of haustrations) were considered to be suggestive, but required further confirmation by a barium enema. The distribution of lesions in the positive cases included 6 in the sigmoid colon, 2 in the cecum, 1 in the transverse colon and 1 in the descending colon. In part, this reflects the general distribution of all the lesions in the 41 patients and undoubtedly, as well, the influence that gravity exerts; *i.e.*, in the supine patient gaseous accumulations outlining these densities tend to be in anteriorly situated portions of the colon.

The majority of patients had a mild increase in the volume of intestinal gas which tended to be equally distributed throughout the small and large bowel as in a nonmechanical ileus. In only 3 of 41 patients did the volume and distribution of gas in the colon raise the suspicion of colonic ob-

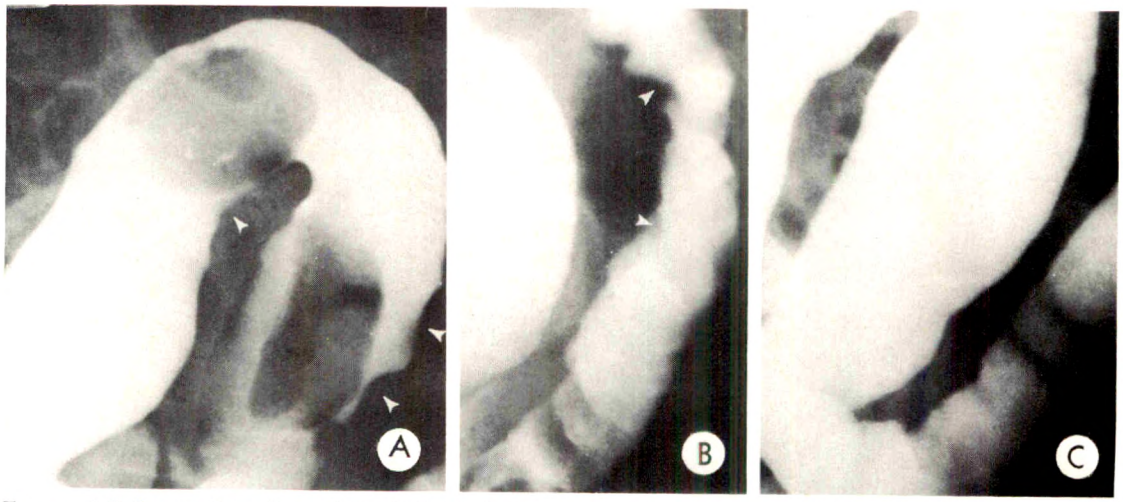

Fig. 3. (*A*) Incomplete distention of distal sigmoid colon demonstrates multiple marginal filling defects (arrows). (*B*) Marginal filling defects (arrows) and mucosal distortion are also evident in the proximal sigmoid colon. (*C*) Complete distention of these segments causes disappearance of these abnormal findings.

struction. In a single patient, the large accumulation of gas in the small bowel suggested a mechanical small bowel obstruction. None of these 4 patients proved to have mechanical obstruction. These findings are in marked contrast to plain film abdominal findings in patients with acute extensive bowel ischemic (AEBI).[28] In the latter group of patients, much larger volumes of gas were present in both the small and large intestine and mechanical obstruction of either was suggested in over 50 per cent of patients.

BARIUM ENEMA EXAMINATION

A barium enema examination was the radiologic procedure which provided the most definitive information concerning the presence and extent of the ischemic process. In 32 of the 39 patients undergoing this examination, evidence of mucosal and/or submucosal inflammatory disease was detected; 6 patients had signs suggestive of an inflammatory process, while in 1 the examination was normal. There was no apparent increase in morbidity associated with this procedure. In the 2 patients in whom extravasation occurred, evidence for preexistent perforation was demonstrated by means of free abdominal gas in one and perirectal abscess in the other. The duration of time between onset of symptoms and performance of the barium enema examination ranged between 12 hours and 23 days. The average duration was 82 hours; 18 were performed within the initial 24 hour period.

The primary radiologic features of ischemic colitis have been shown to be the result of bleeding and edema in the bowel wall and/or sloughing of mucosa.[23] The 2 predominant morphologic radiographic changes are multiple, smooth soft tissue densities often of uniform size in any one patient ("thumbprints") (Fig. 3, *A–C*) and/or diffuse superficial tiny ulcerations (Fig. 4*A*). When the process, as seen at the time of our initial evaluation, was predominantly manifested by "thumbprints," we considered it an exudative process and separated this stage from a predominantly ulcerative one. Although progression from one stage to another is well documented by experimental data,[4,5] such progression was not frequently observed in our clinical material. Shorter intervals between repeated barium enemas may document the true incidence of this phenomenon. As in other inflammatory diseases of the colon, full distention may obscure the findings (Fig. 3,

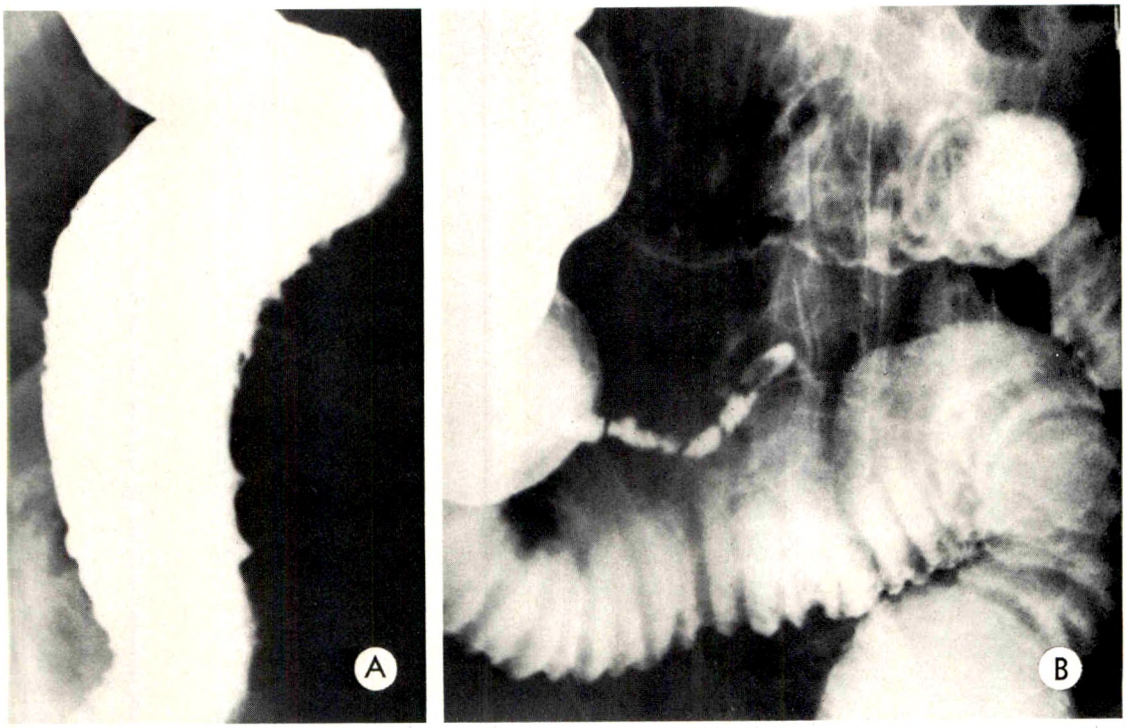

Fig. 4. Common signs of colonic ischemia, in addition to "thumbprints," include: (*A*) multiple superficial ulcerations as seen in the descending colon; and (*B*) transverse ridging in the sigmoid colon which in this patient is located in the right lower quadrant.

A–C), so that careful observation during fluoroscopy and in postevacuation roentgenograms is critical. The exudative process may, instead of localizing as soft tissue densities, result in a more diffuse process producing the less common primary signs: (1) multiple, parallel, thin, lucent, transverse, closely spaced filling defects (Fig. 4*B*) ("transverse ridging"); or (2) thickening and blunting of mucosal folds (Fig. 3*B*). Regardless of the form of intramural disease which occurs, there is frequently rigidity of the bowel wall which is appreciated by the secondary radiographic signs of tubulation and uncoiling of the colon, particularly at the flexures. Spasm, probably a result of the intramural hemorrhage, was commonly present in involved areas, but did not interfere with barium distention of the colon. In 4 patients a portion of ischemic bowel was noted to be flaccid, distended and noncontractile throughout the entire examination. In the 2 of these 4 patients in whom pathologic specimens could be obtained, this area was the site of transmural infarction. The frequency and distribution of the primary and secondary signs as demonstrated on the first barium enema study are tabulated in Table 1.

As in most inflammatory diseases, the barium enema examination was unreliable in the evaluation of the rectum—a site not uncommonly involved.[14] In only 4 of the 10 patients in whom proctoscopy was positive were there radiographic signs of ischemia. However, in the remainder of the colon, this examination was very reliable in defining the extent of the lesion. In only 1 of the 13 patients in whom surgical or autopsy specimens were available was there gross underestimation of the extent of the disease. In this patient, focal areas of necrosis in the ascending and transverse colon were not detected radiographically. In 4 patients with positive proctoscopy, ischemic changes in the descending colon

Table I

INCIDENCE OF RADIOGRAPHIC SIGNS IN 39 PATIENTS

Location and Frequency of Ischemic Process		1				2		
		Thumb-prints	Ulcers	Transverse Ridging	Mucosal Distortion	Spasm	Rigidity	Flaccidity
Cecum	2	1	0	2	0	2	0	0
Ascending Colon	2	2	1	0	1	2	2	0
Transverse Colon	6	5	2	1	1	3	3	0
Descending Colon	21	8	4	4	2	10	4	2
Sigmoid Colon	20	15	8	6	3	14	5	4
Rectum	10	0	3	0	3	3	1	1
Total	61	31	18	13	10	34	15	7

The frequency with which each portion of colon was involved with the ischemic process is listed after the designated segment of colon. Frequently, a segment demonstrated more than one primary and/or secondary sign.

only were demonstrated. Since these patients recovered with conservative management, it is not clear whether this represented a true skip area in the sigmoid colon or a false negative radiographic evaluation. No patient who had a subsequent barium enema study proved to have disease beyond that originally defined.

In spite of the fact that this lesion presents a spectrum of radiologic findings which are often characterized by rapid evolution over short periods of time, it was possible to define a predominant feature for most patients. Such categorization provided prognostic information. Of the 26 patients treated conservatively, 18 recovered and 8 died. When radiographic features of these 2 groups were compared, the following prognostic signs were suggested: (1) little or no resolution in 2 weeks was a poor prognostic sign as was a flaccid or poorly contractile bowel; (2) the presence of a predominantly ulcerative process was perhaps a better prognostic sign than a predominantly exudative process since 7 of 9 patients with the former survived as opposed to 11 of 17 of the latter; (3) the average length of colon in survivors was 35 cm., while in the group that died the average length was 45 cm. In contrast, neither location of the ischemic process nor the duration between onset of symptoms and time of definitive diagnostic study influenced the prognosis.

Diverticulosis was detected in 9 patients and was always present distal to the splenic flexure. The diverticula were all of the scattered type rather than the mass variety. In 4 patients, the diverticula were in the area of the ischemic process, but were not a site of perforation.

Strictures occurred in 4 patients, 3 of whom originally had an exudative form of ischemia. Only 1 of these patients required resection because of obstruction.

ANGIOGRAPHY

Angiography was done in many of these patients because of our initial feeling that occlusive ischemic colitis required different therapy than nonocclusive disease.[30]

Included in the 19 patients studied by angiography were 11 females and 8 males. No specific radiologic selection process was used in the choice of patients for angiography. Their ages ranged from 56 to 89, with an average of 73 years. The interval of time from the onset of symptoms to performance ranged from 16 hours to 45 days with an average of 6 days. Nine examinations were performed within 24 hours and 3 accomplished 15 or more days after the onset of symptoms. Eleven patients eventually recovered without resectional surgery, 7

died, and 1 survived resection of a colonic stricture.

Frontal and lateral abdominal aortograms (Fig. 5, *A* and *B*), using 40 ml. of methylglucamine diatrizoate (Renografin 76), were obtained on 15 patients and this allowed optimal assessment of the origin of the mesenteric vessels. Simple frontal abdominal aortography was used to evaluate the mesenteric vessels in 2 patients and in an additional 2 this was supplemented by a left posterior oblique study. Of these 4, the proximal mesenteric vessels were adequately evaluated in 3.

Seven patients had selective angiography of the inferior mesenteric artery (IMA), using 15 ml. of Renografin 76 and the inferior mesenteric vein (IMV) and tributaries were visualized in all (Fig. 6, *A* and *B*). The rate of injection for the inferior mesenteric arteriography was 3–4 ml./sec. and the fastest filming occurred at 2 ml./sec. carried out over 30 seconds. Five additional patients had a low mid-stream aortogram and this allowed adequate evaluation of the IMA and its branches and in 1 of these patients the IMV was adequately evaluated. Ten of the 19 patients had selective angiography of the superior mesenteric artery (SMA), using 50 ml. of Renografin 76, and in all the superior mesenteric vein (SMV) was seen. In the remaining patients, either or both mesenteric arterial circulations were evaluated simply by conventional aortography and thus only the proximal portions of the main branches could be appreciated without evaluation of the venous circulation. Figure 7 illustrates the distribution of the colonic lesions and the predominant circulation to the involved areas. The average length of affected colon was 35 cm. with 8 having greater than 40 cm. involved.

Considering the average age of the patients examined, arteriosclerotic involvement of the aorta was less than expected either in comparison to random autopsy examinations[20] or a similar age group with the nonocclusive form of AEBI.[32] Angiographically, 6 patients showed no evidence of atherosclerosis and in only 4 of the 19 patients was it judged as moderate or severe. In 1 of these 4 patients the aorta distal to the renal arteries was completely occluded. Of the 17 patients in whom the common iliac arteries could be evaluated, 1 had marked narrowing just beyond the bifurcation and 3 had unilateral narrowing no greater than 50 per cent of the projected diameter. The internal iliac arteries were obstructed unilaterally in 1 patient, slightly narrowed bilaterally in 2, and in 10 were not narrowed at all.

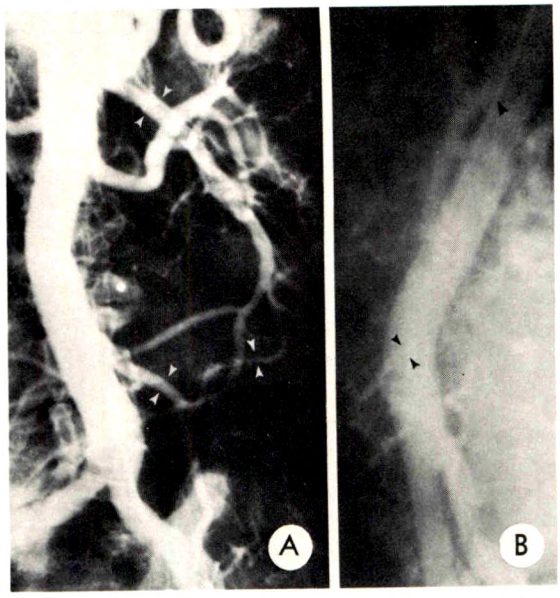

Fig. 5. (*A*) Frontal and (*B*) lateral aortograms of patient with ischemic colitis of the descending colon demonstrating lack of narrowing of the mesenteric arteries at their origin (black arrows) as well as more distally (white arrows). Note also the minimal amount of arteriosclerotic changes in the aorta of this 80 year old woman.

The proximal IMA was occluded in a single patient, decreased in diameter by 50 per cent or more in 2, and by 20 per cent or less in 2, normal in 14. The proximal SMA was normal in 17 patients, decreased in diameter by 25 per cent in 1 and occluded in 1. Two patients had occlusion of the distal SMA resulting in the formation of collateral circulation, but in neither of these 2 patients was there ischemia of the proximal

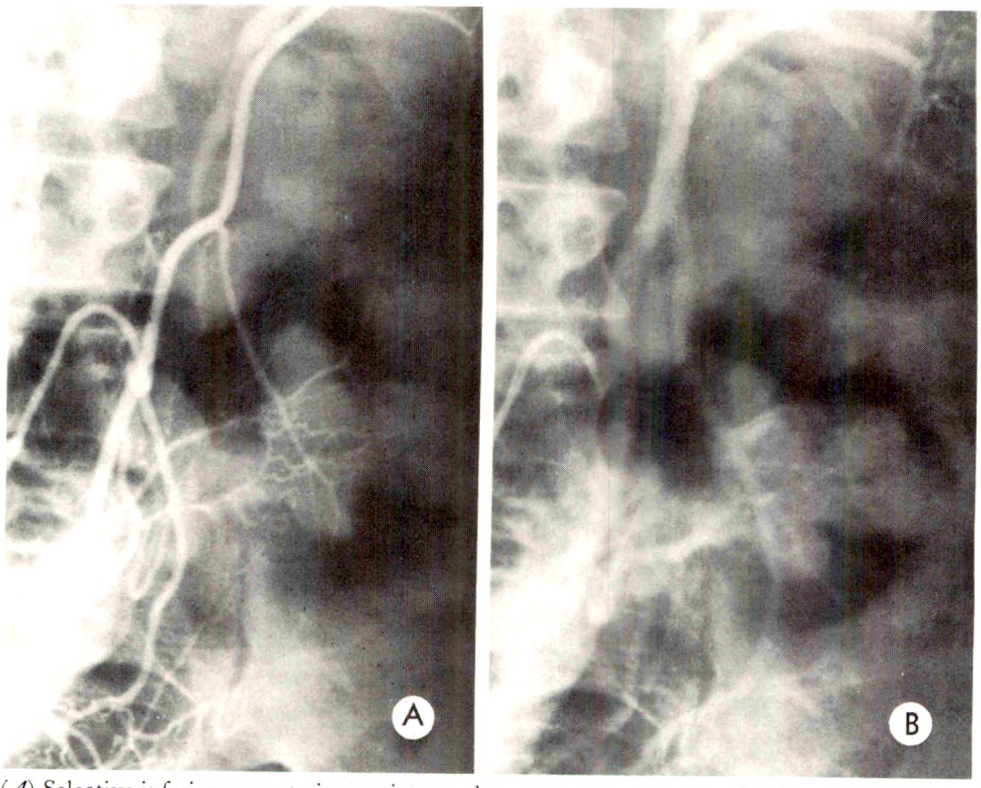

Fig. 6. (*A*) Selective inferior mesenteric arteriogram demonstrates patent vessels of normal caliber including the sigmoid branches which are directly supplying the area with "thumbprints." (*B*) Normal inferior mesenteric vein and tributaries.

colon. In no case were collateral circuits identified as a result of IMA or middle colic artery arteriosclerosis. While angiographic observations cannot be directly compared to autopsy studies of the mesenteric circulation, they suggested that in our group of patients there was a lower incidence of arteriosclerosis than in this general population. Reiner *et al.*,[20] in an autopsy study of population similar in age to the present series, reported 81 per cent incidence of arteriosclerosis in the SMA circulation and 51 per cent in the IMA circuit; 49 per cent of their population had stenosis of the main stem of the SMA, while 38 per cent had stenosis in the main stem of the IMA; 9 per cent had SMA occlusion, while 6 per cent had IMA occlusion. Demos *et al.*[9] noted, in an autopsy survey of 42 patients, that the IMA was stenosed or occluded in 65 per cent and similar abnormalities of the SMA were present in 35 per cent. Kahn and Abrams[13] reviewed the IMA patterns in 136 angiograms obtained for a variety of indications other than intestinal ischemia. In spite of a much larger number of younger patients in this group, the incidence of arteriosclerotic involvement was similar to that in our group of patients. They noted IMA occlusion in 6.6 per cent and "stenosis or atheromatous change of a significant degree" in 17 per cent. Further comparisons with the norms established by Kahn reveal no significant difference in the level of origin of the IMA or the variations in its vascular anatomy or distribution. As illustrated in Figure 8, the diameters (including an estimated 10 per cent magnification factor) of the IMA and its main branches in our series were in general agreement with those of Kahn and Abrams.[13]

The distal inferior mesenteric arterial and inferior mesenteric venous circulations were completely evaluated in 8 patients, 7

of whom had a duration of symptoms averaging 44 hours. Four patients were studied within 24 hours. The eighth patient had angiography performed 23 days after the onset of symptoms when a stricture was documented. Three of 8 patients had vasa recta which appeared dilated (Fig. 9*A*); in the remaining 5 their caliber was considered to be normal (Fig. 9*B*). Reuter *et al.*[21] reported similar dilatation of the vasa recta in their 2 patients with ischemic colitis, 1 of whom had partially occluding emboli. Baum[2] has also reported a patient with similar increased vascularity of the colon as a result of hypersensitivity vasculitis.

In none of our patients was there evidence of spasm or emboli in either the larger named branches or the observed intramural vessels. In 4 patients, arterio-

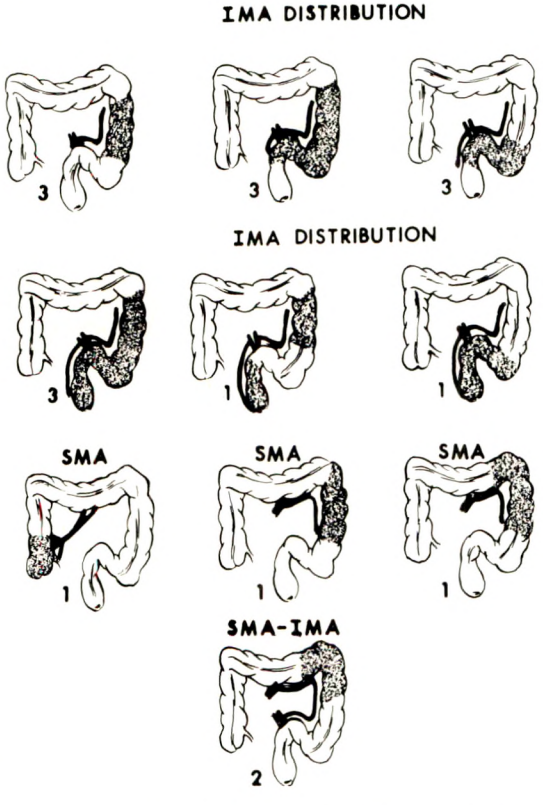

Fig. 7. Distribution of colonic ischemia correlated with the mesenteric arterial circulation as determined by angiography. Note the predominance of lesions largely in the distribution of the inferior mesenteric artery (74 per cent).

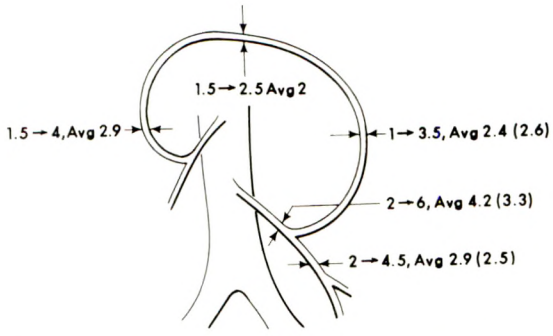

Fig. 8. Diagrammatic representation of the mesenteric circulation to the colon beyond the mid transverse colon. The numbers represent the width of the vessels in millimeters as measured at points designated by the arrows. Both range and averages are given. The numbers in parentheses represent the average width in millimeters for the same vessels as determined by Kahn and Abrams. It is apparent that vasospasm of the middle colic artery or inferior mesenteric artery and its branches could not be documented as the cause of the decreased flow.

venous transit time was $4\frac{1}{2}$, 5, 5 and $5\frac{1}{2}$ seconds, which is less than the lower limit of the normal 6 to 7 seconds established by Kahn and Abrams.[13] In none of these 4 patients was the catheter situated in the wedged position. No venous occlusions were detected and there was no apparent decrease in the diameter of these vessels. Our impression was that the mural veins were more intensely opacified than usual.

The capillary phase was considered unusual in 2 patients because of a nonhomogenous staining of the thickened bowel wall. In both patients, the greater amount of opacification was observed on the luminal side of the wall with little opacification of the serosal half (Fig. 10, *A* and *B*).

CONCLUSIONS

Our experience with these cases of spontaneous ischemic colitis and a group of patients having extensive bowel ischemia[32] establishes an important difference in the incidence of the underlying vascular etiologies of the 2 major categories of primary ischemic disease of the intestine. Based on this information and a dramatic difference in the prognosis of the 2 diseases, we have

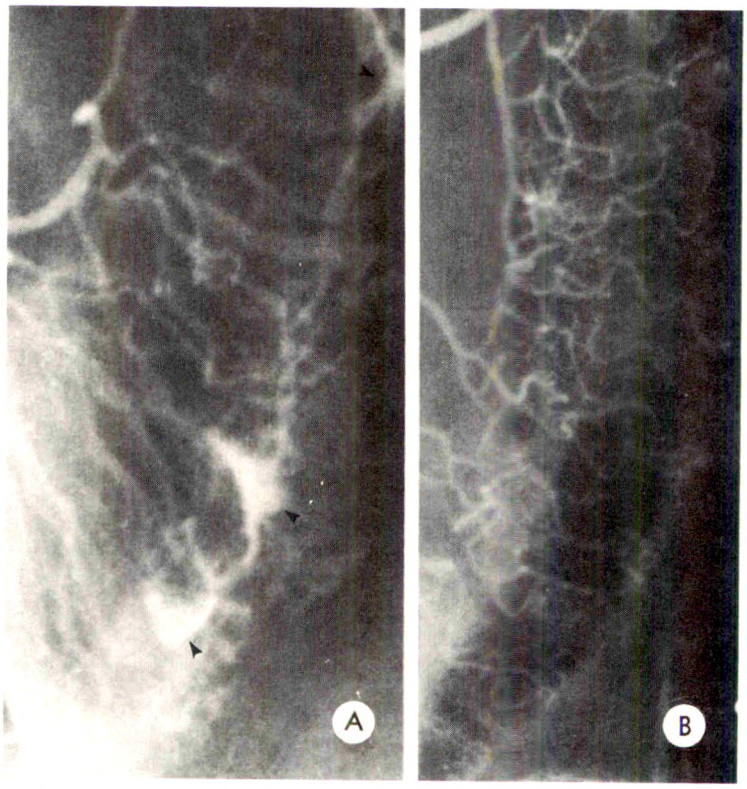

FIG. 9. (*A*) Close-up view of the dilated vasa recta supplying a portion of the sigmoid colon demonstrated on barium enema examination to have ischemic changes (arrows point to residual barium in the colonic lumen). (*B*) Close-up view of normal caliber vasa recta in segment of ischemic descending and sigmoid colon.

evolved a contrasting diagnostic and therapeutic approach.

AEBI is a disease primarily of the SMA distribution. On occasion the left side of the colon is concomitantly involved in the nonocclusive variety. This form of the disease is often associated with congestive heart failure, digitalis toxicity and/or peripheral occlusive arterial disease. Characteristically, the clinical picture is one of severe abdominal pain, vomiting and/or diarrhea and gastrointestinal bleeding. These signs are followed by hypovolemia, abdominal distention, peritonitis and shock. The prognosis is extremely poor. In a previous report,[32] we have defined the spectrum of etiologies causing this disease and have outlined a comprehensive radiologic approach to such patients. Fundamental to this scheme is the performance of an emergency arteriography to determine the patency of the SMA. Approximately one-half of such patients are found to have a patent mesenteric circulation and are considered to have a low flow state. Since vasospasm is thought to account, in part, for this ischemic process and has been angiographically demonstrated by us in 50 per cent of these patients, intraarterial vasodilators would seem to be a rational therapeutic measure[1] and has been successful in 2 of our last 4 such patients. In contrast, SIC presents clinically as a far less devastating disease and is usually unaccompanied by an obvious precipitating cause.[31] The pain, rarely more than mild, is located in the lower abdomen usually on the left. On occasion, the pain is fleeting enough to be ignored by the patient unless closely questioned. Although bloody diarrhea is common, blood loss and

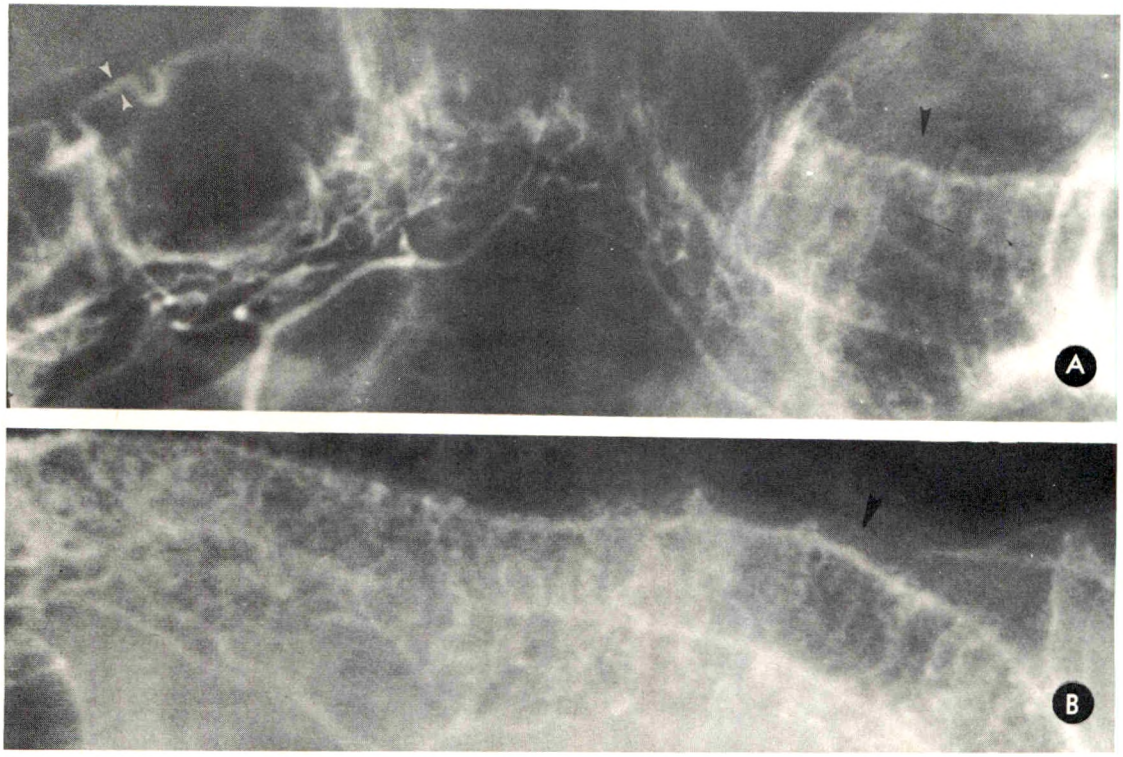

Fig. 10. (*A*) Capillary phase of patient illustrated in Figure 9*B*. Large black arrow denotes outer margin of the thickened bowel wall. Note the preferential accumulation of contrast material towards the luminal side of the wall. (*B*) The findings in the distal descending colon (black arrow) are similar to those in *A*. The more proximal unaffected colon (white arrows) shows the usual thickness of bowel wall with a normal homogenous staining.

volume depletion are not a therapeutic problem. Endoscopy can be helpful in defining an inflammatory mucosal lesion as it was in 17 patients in our series. In only one of the 41 cases in this study was the original clinical impression that of AEBI.

The plain film abdominal roentgenogram may provide useful information for distinguishing between these 2 diseases. The volumes of intestinal gas and fluid are much less in SIC than AEBI, the former usually appearing as a mild nonmechanical ileus, the latter in one-half of the cases as mechanical intestinal obstruction.[28] Although the incidence of positive plain film roentgenographic diagnosis is approximately 20 per cent in both diseases, there is very little overlap in the distribution of the positive roentgenographic signs. Of the 67 patients with extensive ischemic disease reviewed by Tomchick *et al.*,[28] 43 had involvement of the colon, but only 1 patient exhibited positive radiographic signs in the colon *per se*. None of the patients in the present series documented false radiographic evidence of small bowel ischemia.

If clinical, laboratory, preliminary radiographic and/or endoscopic information allow a diagnosis of ischemic colitis, the next appropriate procedure is a barium enema examination. This should be performed as soon as the diagnosis is suspected to confirm the presence of the disease and its extent, to exclude an unsuspected co-existent obstructing colonic lesion and to provide prognostic information. Our results indicate that the barium enema study is a reliable test for defining the location of the disease in the areas of the colon other than the rectum. This definition of the extent of

the disease is vital if resection is to be undertaken, since mucosal and submucosal ischemia may be overlooked at surgery if unaccompanied by evidence of serosal ischemic changes.

It should be noted that the accuracy of the barium enema examination may be overstated because of the strict criteria used to define our patients with SIC. Also, we suspect that less severe cases of colonic ischemia occur in which the clinical diagnosis is considered, but a "negative barium enema" allows the patient to go undiagnosed. There are, as well, a group of patients, who present with rectal bleeding and initially have equivocal radiographic findings. In this group, as well as all patients with recently diagnosed ischemic colitis treated conservatively, a repeat barium enema study in 5 to 7 days is vital to define the evolution of the radiographic findings. In the patient with equivocal changes, newer findings may suggest an ischemic etiology; in the well defined ischemic group, the classical evolution is reassuring diagnostically. Barium enema examinations should be repeated every 8 to 10 days, until complete resolution has occurred or a stricture with a constant diameter has been established.

A great deal of confusion exists in the literature as to the exact etiology of SIC. While Boijsen[3] states "in many cases an occluded artery was found at autopsy or operation, but occasionally, no occlusion was observed at angiography," Boley and Schwartz[4] say "although a cause of colonic ischemia, or a site of occlusion, frequently has been recognized, no specific etiology or occlusion has been identified in the majority of cases." Underlying the confusion are several problems: (1) the paucity of angiography in cases of SIC; (2) the unreliability of the evaluation of vascular patency during surgery; (3) the technical inability to properly evaluate the vasculature of a resected segment of colon; (4) the inability to determine the chronicity of vascular obstruction at autopsy without careful multiple postmortem injections; and (5) the dilemma of whether observed small vessel thromboses antedate or postdate the tissue necrosis. Angiography is an excellent tool for evaluating the major IMA and IMV systems and the vasa recta circulation; chronicity of vascular obstruction can also be inferred by the definition of collateral circulation. Of 19 previously reported cases of SIC with angiography, 10[10,11,17,19,21,26,27,29] were accompanied by arterial occlusion, stenosis and/or emboli and 9[7,8,12,14,19,21,25] showed uncompromised mesenteric arterial circulations. In our original description,[30] 4 patients who fulfill our present criteria for SIC had a patent arterial circulation. Our experience with an additional 15 patients would strongly support the conclusion that the large majority of patients with SIC do *not* have major vessel occlusive arterial disease. Additionally, in 8 patients in whom it was evaluated, the inferior mesenteric venous system was normal. As well, the absence of venous thromboses in our resected specimens would argue against this circuit being the etiologic site of the disease. These data establish the fact that arteriography does not provide the therapeutic implication we suspected in earlier studies[30] and thus angiography is not a critical part of the diagnostic approach to SIC. Such studies have, however, helped delineate some of the features of the pathogenesis of this disease.

The results suggest that *if* the basis of the disease presently called "ischemic colitis" is, in fact, ischemia, it is likely a result of alterations in flow or perfusion within the bowel wall itself. Based on our angiographic documentation, the popular "watershed" theory of ischemia commonly affecting the colon at the junction of the IMA and SMA circulation is untenable. In 14 of the 19 patients undergoing angiography, the ischemia was in the portion of the colon directly supplied by the IMA and in only 2 was ischemia present at the junction of the mesenteric circulation. Certainly, a precedent for ischemia resulting from perfusion abnormalities exists in the entity of extensive nonocclusive ischemia of the

small intestine in which the pathophysiology has been more clearly elucidated.[31] It is unclear, however, whether the exact same pathogenesis can be invoked for SIC. The age and racial distributions are similar in the 2 categories of diseases. However, dissimilarities also exist which fail to completely support this analogy. Many patients with the nonocclusive variety of AEBI suffer from an acute episode which is followed by redistribution of cardiac output. We have angiographically documented the presence of arterial vasoconstriction in the presence of this disease[32] and this has led us to use vasodilators as a therapeutic measure.[1] On the other hand, the large majority of our patients with SIC do not have a well defined prodrome leading to altered cardiac output nor was there evidence of such by clinical parameters. In none of the patients was vasospasm defined in either the major vessels or the vasa recta. When the latter vessels were evaluated, they were either normal in caliber or dilated. The significance of vasodilatation is unclear, since it could be argued that a period of vasospasm pre-existed the angiographic demonstration of vasodilatation. While this may be true, our experience in the nonocclusive form of AEBI has demonstrated the existence of spasm over a symptom duration greater than 24 hours,[32] which is the symptom duration within which 9 of our patients in the present series were examined. Angiography of other inflammatory diseases of the colon has shown similar characteristics including vasodilatation and decreased transit time.[7] While one could argue that because of these similarities, "ischemic colitis" is really idiopathic ulcerative colitis occurring in the elderly, a more likely explanation is that the bowel vascularity has only a very limited capacity of reacting to a number of different noxious stimuli. Bosniak[6] has described and illustrated the effect of vasodilators on the spastic vasa recta of the dog colon. It is of interest that his findings resemble those in 2 of our patients in whom a redistribution of contrast material to the luminal side of the bowel wall occurred. Interpreted in teleologic terms, these findings would suggest preferential flow to the more superficial mucosal and submucosal layers which are the most vulnerable to hypoxic conditions. Since in both these patients simultaneous recovery occurred without stricture formation, a tolerance of such a state by the muscular layers is suggested.

Is there really a disease entity of "ischemic colitis"? The experimental work of Boley *et al.*,[5] observations made after acute deprivation of colonic blood supply during an abdomino-perineal resection,[33] and 10 cases of occlusive vascular disease in the literature all suggest that there is such a disease. A disease entity pathologically indistinguishable from those with an occlusive etiology would also seem to exist in which no occlusions of the larger vessels are present. The disease affects the distal colon, usually that supplied by the IMA. Our observations do not allow any conclusion of whether this is primarily from redistribution of flow, although such an etiology is suspected. Is the distinction between occlusive and nonocclusive forms of SIC important? Combining this series of 19 angiography cases with the previously reported 16, the results show that 65 per cent of the occlusive cases and 66 per cent of the nonocclusive cases recover without acute resectional surgery. It can be seen, therefore, that the place of angiography in the diagnosis and treatment of ischemic colitis is to be questioned for several reasons: (1) the incidence of arteriosclerotic changes in this general population is high enough so that often the demonstration of mesenteric arterial obstruction has unknown significance; (2) the demonstration of occlusion or patency of vessels has no clear-cut diagnostic, therapeutic, or prognostic significance; and (3) unlike our findings in AEBI, spasm has not been demonstrated, so there is no rationale for the use of intraarterial vasodilators. While further experience with angiography, particularly techniques allowing evaluation of the microvasculature, may lead to continued elucidation of a

pathophysiologic mechanism, it is not considered to be an essential procedure in the diagnosis of SIC.

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BENIGN FORM OF NECROTIZING ENTEROCOLITIS*

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THE radiographic findings in neonatal necrotizing enterocolitis have been previously described.[2,3,7] These include bowel dilatation, pneumatosis intestinalis, portal venous gas and pneumoperitoneum. The typical case will have necrosis of a segment or segments of bowel resulting in perforation. Surgery is then usually considered mandatory. A small series of cases has been described in which infants with necrotizing enterocolitis and pneumoperitoneum were treated medically.[9] Those who survived later required surgery for stricture formation.

There is a smaller group of patients who do not perforate, but have delayed manifestations.[1,3–5,8] In this group, vascular compromise produces stricture formation or internal fistula resulting in bowel obstruction. This also requires surgery.

Finally, there is a third group of patients who have comparatively mild clinical signs and symptoms related to the gastrointestinal tract. These infants demonstrate the radiographic findings of necrotizing enterocolitis except for pneumoperitoneum and do well with medical management. Cases which belong in this group have been alluded to in previous reports.[1,5,6]

The case histories and radiographic findings of 7 cases which can be placed in this latter group will be presented. Because of the clinical course of these infants, we have referred to the disease process in this group as the benign form of necrotizing enterocolitis, representing one end of a spectrum.

REPORT OF CASES

CASE I. PF 328-02-83 is a 1,680 gram female born following a 36 week gestation. The pregnancy was complicated by ruptured membranes 16 days prior to spontaneous vaginal delivery in an outside hospital. Apgars of 7 were obtained at 1 and 5 minutes.

Transient respiratory distress was present on admission 2½ hours after birth. There was no radiographic evidence of hyaline membrane disease. An umbilical arterial catheter was inserted on Day 0 and remained in place for 36 hours. An umbilical venous catheter was placed for a shorter period.

On Day 2, blood-streaked stools were noted. However, the infant remained in normal condition without abdominal distention. A roentgenogram of the abdomen showed pneumatosis intestinalis in the distribution of the descending colon. There was no bowel dilatation.

On Day 3, the infant was placed on antibiotics, and oral feedings were discontinued. The clinical condition was unchanged. Extensive pneumatosis intestinalis was seen in the distribution of the entire colon (Fig. 1*A*). Because of the discrepancy between the clinical condition of the infant and the roentgenogram, a colon study was ordered. A Hypaque enema (Fig. 1*B*) confirmed the presence of the pneumatosis intestinalis.

On Day 6, there was only a small amount of residual pneumatosis intestinalis, and the stools were hematest negative. Oral feedings were resumed, and the infant was discharged 25 days later.

CASE II. PF 332-47-60 is a 1,640 gram male infant born following a 34 week gestation. Spontaneous vaginal delivery was complicated by maternal hemorrhage, probably due to abruptio placentae. Apgars of 6 were obtained at 1 and 5 minutes. The infant had mild transient respiratory distress, treated by oxygen. Chest roentgenograms showed no evidence of hyaline membrane disease. An umbilical arterial catheter was placed on Day 0 and removed 48 hours later.

On Day 2, blood-tinged stools were passed, and gastric residual was noted. The clinical condition otherwise remained normal. Oral feedings were discontinued, and the infant was placed on antibiotics. An abdominal roentgenogram showed slight dilatation of multiple loops of bowel and questionable pneumatosis intesti-

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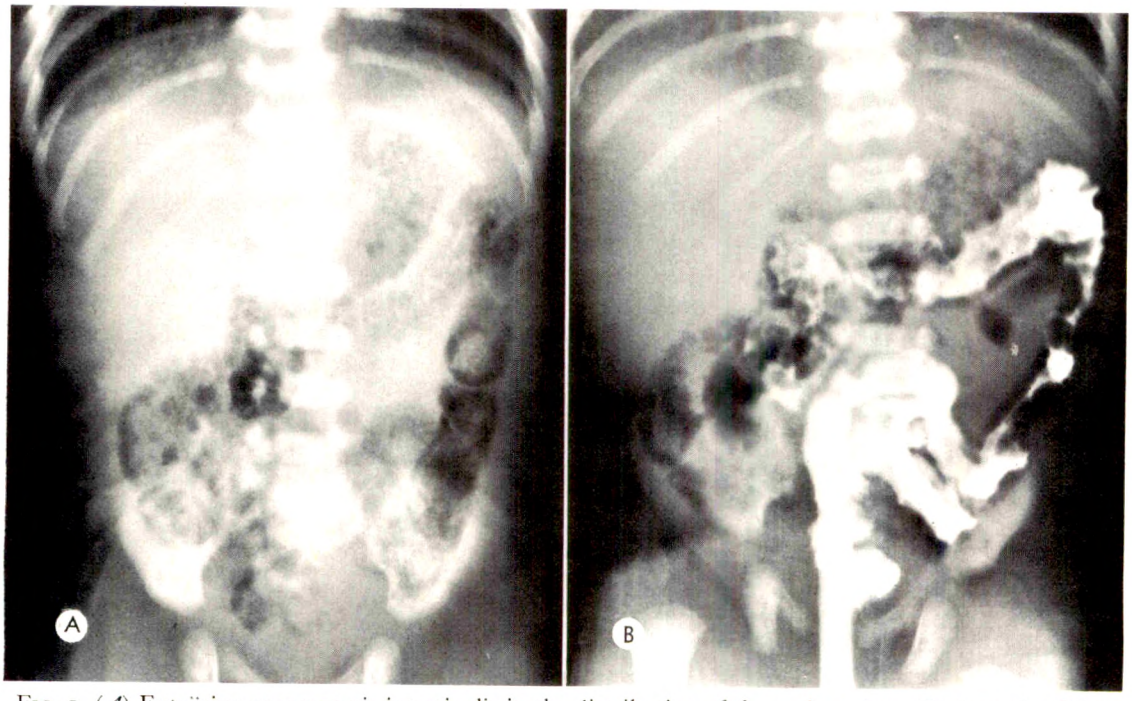

FIG. 1. (*A*) Extensive pneumatosis intestinalis in the distribution of the entire colon. (*B*) Irregular filling defects in the Hypaque enema examination produced by the collections of intramural gas.

nalis on the right side of the abdomen. A lateral roentgenogram (Fig. 2) obtained 8 hours later demonstrated a linear collection of intramural gas in the rectum.

On Day 3, a normal intestinal gas pattern was present. The clinical condition remained good and oral feedings were resumed on Day 4. By Day 7, the stools were hematest negative. The infant was discharged 22 days later.

CASE III. PF 336-11-82 is a 1,290 gram male infant born following a 29 week gestation. The pregnancy was complicated by premature rupture of the membranes 3 days prior to onset of labor. Following vaginal delivery at an outside hospital, the infant had an episode of apnea, treated by positive pressure with mask and bag. Apgar scores were not obtained. The amniotic fluid was described as being mucopurulent.

On admission to the nursery approximately 1 hour after delivery, respiratory grunting and hypothermia were noted. The infant was treated with positive pressure by mask and bag, placed on intravenous fluids, and started on an 8 day course of antibiotics for amnionitis. Blood transfusions were given for a low hematocrit. An umbilical arterial catheter was passed to the level of the right common iliac artery and was maintained in place for less than 24 hours. Chest roentgenograms revealed nodular densities in the lower lungs consistent with mild hyaline membrane disease.

The respiratory distress resolved during Day 1. Oral feedings were begun on Day 2. However, the infant developed abdominal distention with gastric residual and on one occasion vomited a large amount of greenish fluid. Abdominal roentgenograms over a 3 day period (Day 1 through Day 3) showed slight generalized intestinal dilatation. This was thought to represent a nonspecific adynamic ileus or a low grade meconium blockage syndrome. Oral feedings were discontinued for a 6 hour period on Day 3. The distention improved, and the oral feedings were resumed and tolerated well. In subsequent days, the infant fed well by gavage and gained weight.

On Day 12, blood-tinged stools were passed. The abdomen remained soft and nondistended, and no vomiting or gastric residual was observed. Oral feedings were discontinued, and the infant was placed on antibiotics. An abdominal roentgenogram (Fig. 3) demonstrated pneumatosis intestinalis in the distribution of the descending and sigmoid colon, without bowel dilatation. By Day 15, the pneumatosis intes-

tinalis had resolved. The clinical condition during this period was unremarkable. Oral feedings were resumed and by Day 20, the stools had become hematest negative. The infant was discharged at 8 weeks of age.

Case IV. PF 346-62-69 is an 1,140 gram male infant born following a 28 week gestation. Delivery was by version extraction of a double footling breech presentation under general anesthesia. Apgars of 2 and 5 were obtained at 1 and 5 minutes. The infant received oxygen by mask for transient cyanosis. Umbilical venous and arterial catheters were placed shortly after admission to the nursery. At this time the infant had mild tachypnea and some retractions, but the chest roentgenogram was normal. The infant was treated with 25 per cent oxygen and intermittent positive pressure by mask and bag. The umbilical venous catheter was removed on Day 4. Transfusions of packed red blood cells were given on Days 5 and 6 for a low hematocrit. The arterial catheter was removed on Day 8.

On Day 12, the infant passed a grossly bloody stool. However, there was only slight abdominal distention, and oral feedings were tolerated. A roentgenogram of the abdomen (Fig. 4) demonstrated slight to moderate dilatation of small and large bowel loops and extensive pneumatosis intestinalis in the distribution of the entire colon.

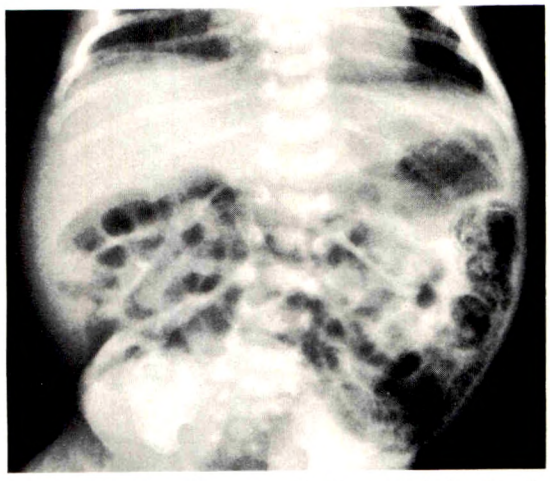

Fig. 3. Case III. Pneumatosis intestinalis in the distribution of the descending and sigmoid colon.

On Day 13, the clinical status and radiologic findings were unchanged. However, by Day 15, gastric residual and poor skin color were observed. Stools were hematest positive. Antibiotics were begun, and oral feedings were discontinued. An abdominal roentgenogram

Fig. 2. Linear collection of intramural gas in the rectum.

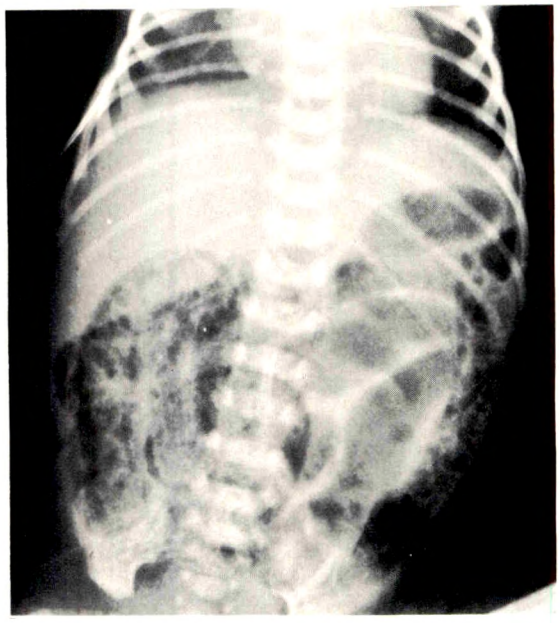

Fig. 4. Case IV. Extensive pneumatosis intestinalis in the distribution of the entire colon. Slight to moderate dilatation of the intestinal loops.

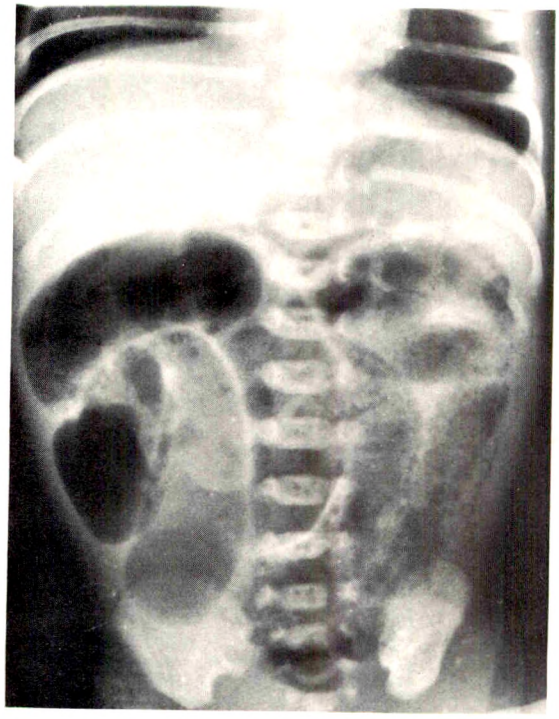

FIG. 5. Case v. Dilated intestinal loops, bubbly collections of intramural gas, and portal venous gas.

showed no bowel dilatation, but pneumatosis intestinalis was again seen in the entire colon.

On Day 16, the stools became hematest negative, and there was incomplete resolution of the pneumatosis intestinalis. Transfusions of packed red blood cells were given as the hematocrit had dropped from 39 on day 9 to 27 on Day 15. Oral feedings were resumed on Day 19. An abdominal roentgenogram on Day 23 showed a normal intestinal gas pattern. The infant was discharged at 2 months of age.

CASE V. PF 350-60-18 is a 1,480 gram female infant born following a 30 week gestation and spontaneous rupture of membranes 24 hours prior to delivery. Delivery was by cesarean section for breech presentation. Apgars of 2 and 6 were obtained at 1 and 5 minutes. The infant required positive pressure resuscitation with mask and bag and subsequently, 60 per cent oxygen by hood for respiratory distress during the first 3 days. There was no radiologic evidence of hyaline membrane disease. Umbilical venous and arterial catheters were placed on Day 0 and removed within 48 hours and 72 hours, respectively.

On Day 4, the infant developed abdominal distention, vomiting, and lethargy. Stools were initially blood-tinged and then hematest positive. An abdominal roentgenogram (Fig. 5) demonstrated moderate dilatation of multiple loops of bowel with extensive pneumatosis intestinalis and portal venous gas. The infant was placed on antibiotics, and oral feedings were discontinued.

By Day 5, the intestinal dilatation persisted, but the pneumatosis intestinalis and portal venous gas had resolved. Blood transfusions were given because of a drop in hematocrit from 49 per cent on Day 0 to 33 per cent on Day 5.

The clinical condition improved, and by Day 8 the intestinal gas pattern was normal. Stools became hematest negative on Day 9. The infant was discharged at 9 weeks of age.

CASE VI. PF 351-94-31 is a 2,470 gram female infant born following a 37 week gestation. A normal vaginal delivery followed artificial rupture of amniotic membranes for low grade RH sensitization. Apgars of 8 and 9 were obtained at 1 and 5 minutes. Oxygen was given by mask and hood for transient respiratory distress. A chest roentgenogram was normal. An umbilical arterial catheter was placed on Day 0 and was removed on Day 2, because of vascular insufficiency to the left leg. This subsequently resolved. On Day 3, the infant developed abdominal distention and passed a blood-streaked stool. Abdominal roentgenograms (Fig. 6, *A* and *B*) revealed slight dilatation of bowel loops, pneumatosis intestinalis on the right side of the abdomen, and portal venous gas. The infant was placed on antibiotics, and oral feedings were discontinued.

By Day 4, the abdomen was soft; the stools were hematest positive. Transfusion of packed red blood cells was given because of a drop in hematocrit from 38 per cent on Day 3 to 31 per cent on Day 4. An abdominal roentgenogram revealed a normal intestinal gas pattern except for slight dilatation of some loops.

On Day 5, a normal gas pattern was present. Oral feedings were resumed on Day 6, and the stools became hematest negative on Day 9. The patient was discharged at 15 days of age.

CASE VII. PF 357-48-30 is a 1,740 gram male infant born following a 30 week gestation. The

pregnancy was complicated by an episode of vaginal bleeding and maternal fever 12 hours prior to delivery. Delivery was by cesarean section for placenta previa and transverse lie. Apgars of 8 and 10 were obtained at 1 and 5 minutes. The infant had no respiratory distress, and a chest roentgenogram was normal. An umbilical arterial catheter was passed and remained in place for 5 days.

On Day 2, the infant developed abdominal distention and lethargy. Hematest positive stools were passed. An abdominal roentgenogram (Fig. 7) demonstrated bowel dilatation, pneumatosis intestinalis involving the stomach and intestinal loops on the right side of the abdomen, and portal venous gas. Oral feedings were discontinued, and the infant was placed on antibiotics.

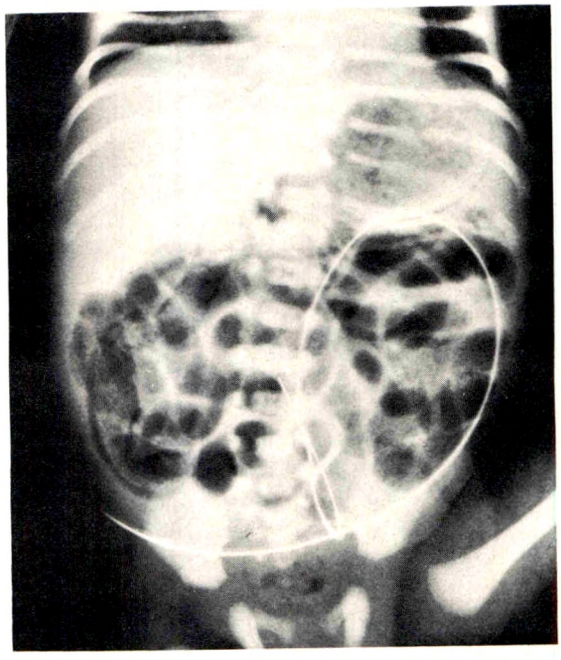

Fig. 7. Case VII. Slight dilatation of intestinal loops, curvilinear collections of intramural gas involving the stomach and intestinal loops on the right side of the abdomen, and portal venous gas.

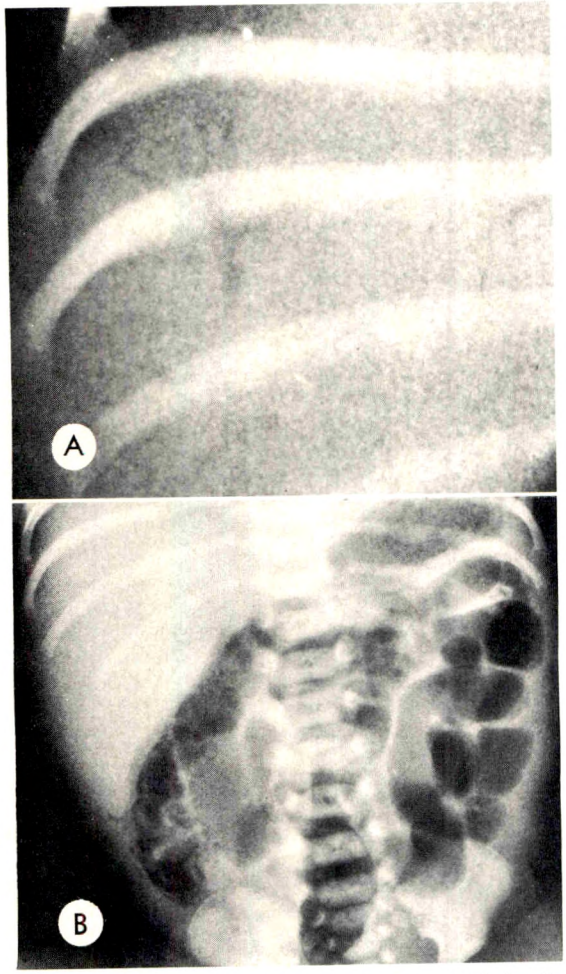

Fig. 6. Case VI. (*A*) Portal venous gas. (*B*) Slight dilatation of intestinal loops. Pneumatosis intestinalis on the right side of the abdomen.

The following day, the intestinal gas pattern was unremarkable except for slight dilatation. On Day 4, the infant was more active and less distended, and the stools became hematest negative. A normal intestinal gas pattern was present on Day 5, and oral feedings were resumed on Day 6. The patient was discharged at 28 days of age.

Comment. In the 7 cases presented, all of the infants were premature by weight and gestation. Only 1 infant (Case III) had hyaline membrane disease, and this was clinically mild. With the development of necrotizing enterocolitis, Cases I, II, and III were clinically normal, except for the presence of blood in the stools. The remaining cases were more symptomatic with abdominal distention, lethargy, gastric residual, and vomiting, in addition to bloody or hematest positive stools. Blood and stool cultures were negative for pathogenic organisms in all of the infants.

Cases I and III demonstrated pneumatosis intestinalis only. Cases II and IV had bowel dilatation in addition to pneumatosis intestinalis.

Cases v, vi and vii demonstrated a combination of bowel dilatation, pneumatosis intestinalis, and portal venous gas.

DISCUSSION

From the cases presented, it can be seen that bowel dilatation, pneumatosis intestinalis, and portal venous gas may be present in the neonatal period without progression to significant bowel necrosis. Because the radiographic appearance seen in our series of cases is that usually associated with neonatal necrotizing enterocolitis and because of the clinical signs and symptoms related to the gastrointestinal tract, we believe it is justified to consider this group in the category of necrotizing enterocolitis.

In those infants in whom bowel dilatation is present with pneumatosis intestinalis and sometimes portal venous gas, a definite prognosis cannot always be made. The majority of these cases will develop significant bowel necrosis. Three of the cases presented are examples which did not progress to significant necrosis.

It is evident that the presence of portal venous gas is not an indication for surgical intervention in necrotizing enterocolitis. This decision should be based on the presence of a pneumoperitoneum or clinical deterioration of the infant.

In those infants in whom pneumatosis intestinalis is present without bowel dilatation, the most likely prognosis is that of the benign form of necrotizing enterocolitis. This statement is based on our experience with 78 cases of necrotizing enterocolitis in the last 3 years. Two of the cases presented are examples in which the benign prognosis may certainly be suggested.

The etiology for the benign form of necrotizing enterocolitis is unknown but may be related to transient intestinal hypoxia.

Finally, it should be mentioned that the radiographic appearance of necrotizing enterocolitis is nonspecific and may be seen in other entities in the neonatal period which produce bowel necrosis, such as mesenteric arterial or venous occlusion or intestinal volvulus.

SUMMARY

Significant bowel necrosis does not occur in the benign form of necrotizing enterocolitis.

Seven cases are presented which can be placed in this category.

The radiographic findings in this group include bowel dilatation, pneumatosis intestinalis, and portal venous gas.

A benign prognosis may be suggested when pneumatosis intestinalis is present without bowel dilatation.

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EVALUATION OF BARIUM AND GASTROGRAFIN AS CONTRAST MEDIA FOR THE DIAGNOSIS OF ESOPHAGEAL RUPTURES OR PERFORATIONS

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SINCE the description by Boerhaave of the fate of Admiral Baron van Wassenaer, who suffered a spontaneous tear of the esophagus,[22] progress in surgery has greatly improved the prognosis in this previously fatal condition.[6,7,23] These improvements were hallmarked by Sencert's first surgical cure, Overholt's thoracotomy and drainage, and Barrett's first successful closure of the esophagus.[4] Most esophageal perforations are due to iatrogenic instrumentation or paraesophageal operations.[11,25] Other causes of esophageal perforation are foreign bodies, external trauma and chemical injury.[27,37–39] Rupture of the esophagus may occur spontaneously in the normal (emetogenic) or previously diseased esophagus due to rapid localized increase in intraluminal pressure.[5,24,28,30]

Most reports concerning the clinical manifestations and treatment of transluminal esophageal tears stress the importance of early detection and prompt surgical intervention. Opinions vary as to the appropriate contrast agent for use in clinical investigation in suspected perforation of the esophagus. Iodinated oily or water soluble contrast media are most frequently recommended.[8,14,23] Some authors consider the utilization of barium to be contraindicated based upon the belief that the presence of foreign material in the infected mediastinum will potentiate the inflammatory process.[2,27,29] This concept is based upon isolated observations or extrapolated from the experience with perforation of the abdominal viscera during barium study. There is believed to be additional deleterious effect of barium in the peritoneal cavity. However, animal experiments investigating the exposure of the peritoneum to barium and bacterial flora are not in full agreement.

Recognizing the advantages of barium sulphate with regard to its physical properties, we compared its effects upon the mediastinum with the most commonly employed water soluble contrast medium. The purpose of this study was to evaluate the effects of barium and Gastrografin on the mediastinum of an animal model either alone or in combination with bacterial culture of pooled human flora to create mediastinitis. Clinical and histologic studies were performed to evaluate the relationship of these mixtures upon the production and severity of mediastinitis.

MATERIAL AND METHOD

A. ANIMAL MODEL

Because of the presence of a "complete" mediastinum, the demonstrated similarity of reaction to human flora, and the histologic correlation, domestic short haired adult cats (5–7 kg.) were utilized for this study. Thirty cats were divided into groups

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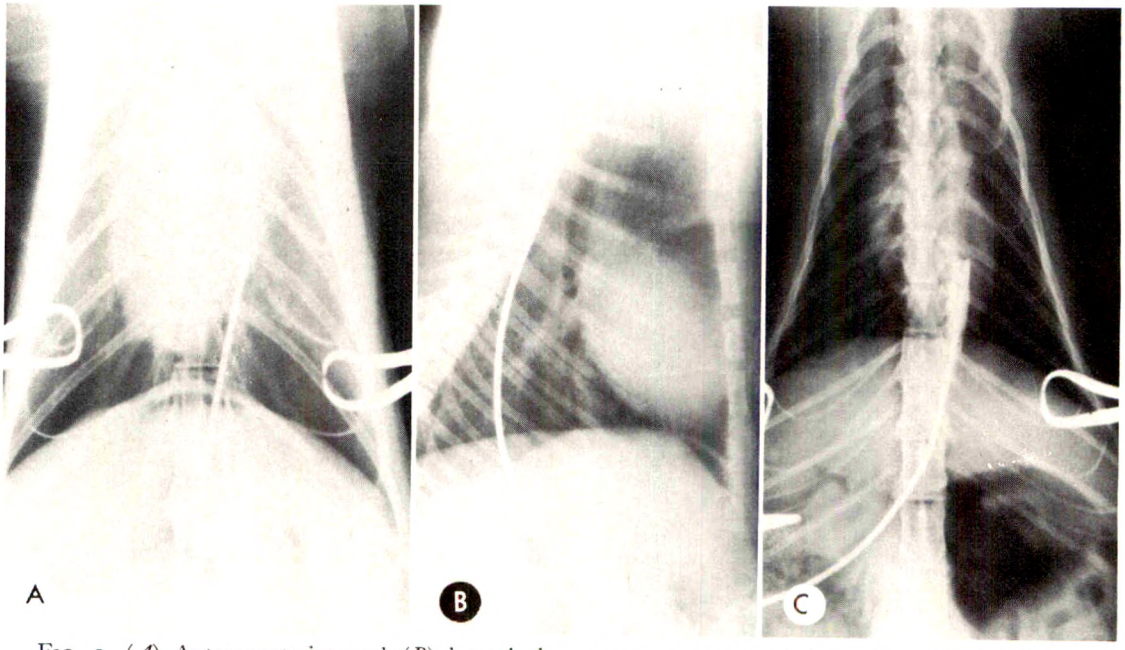

FIG. 1. (*A*) Anteroposterior and (*B*) lateral chest roentgenograms to determine proper catheter placement. (*C*) Anteroposterior chest roentgenogram at time of injection.

depending upon the substance injected into the mediastinum.

Group I —Operative Controls
Group II —Commercial Barium
Group III —Sterile Barium Sulphate U.S.P.
Group IV —Gastrografin
Group V —Flora
Group VI —Gastrografin+Flora
Group VII—Barium+Flora

B. EXPERIMENTAL PROCEDURE

The injection into the ventral caudal mediastinum was made through an abdominal approach. Following an upper medial laparotomy incision a slit was made in the anterior proximal end of the abdominal esophagus to allow introduction of a smooth tipped semirigid catheter into the mediastinum (Fig. 1, *A–C*). The catheter was advanced carefully along the subserosal layer for approximately 2.5 cm. Care was taken not to perforate the delicate mediastinal pleura. The injection with fluoroscopic monitoring was performed slowly to permit dissection of the adjacent tissue.

After injection of the material, the site of insertion of the catheter in the esophagus was sutured with No. 000 chromic catgut and the abdominal incision was closed in a routine manner. The animals were monitored clinically and with chest roentgenograms (Fig. 2, *A* and *B*) in the postoperative period and were sacrificed at varying intervals from 2 to 90 days. Additionally, chest roentgenograms were obtained prior to sacrifice to see if there was parenchymal reaction in the lungs, to detect possible extravasation of the contrast medium into the pleural space (Fig. 3), and to determine if mediastinal irregularity and widening had occurred.

A total volume of 1 cc. was inoculated each time. To produce mediastinitis, a 24 hour culture of pooled human mouth flora containing approximately 5×10^8 bacteria, assessed by turbidometry and pour-plate technique, was used as the inoculum. This flora contained coliform and proteus organisms, gram positive aerobic spore forming bacilli, microaerophilic and anaerobic streptococci and lactobacilli (Table 1). This concentration was found to produce histo-

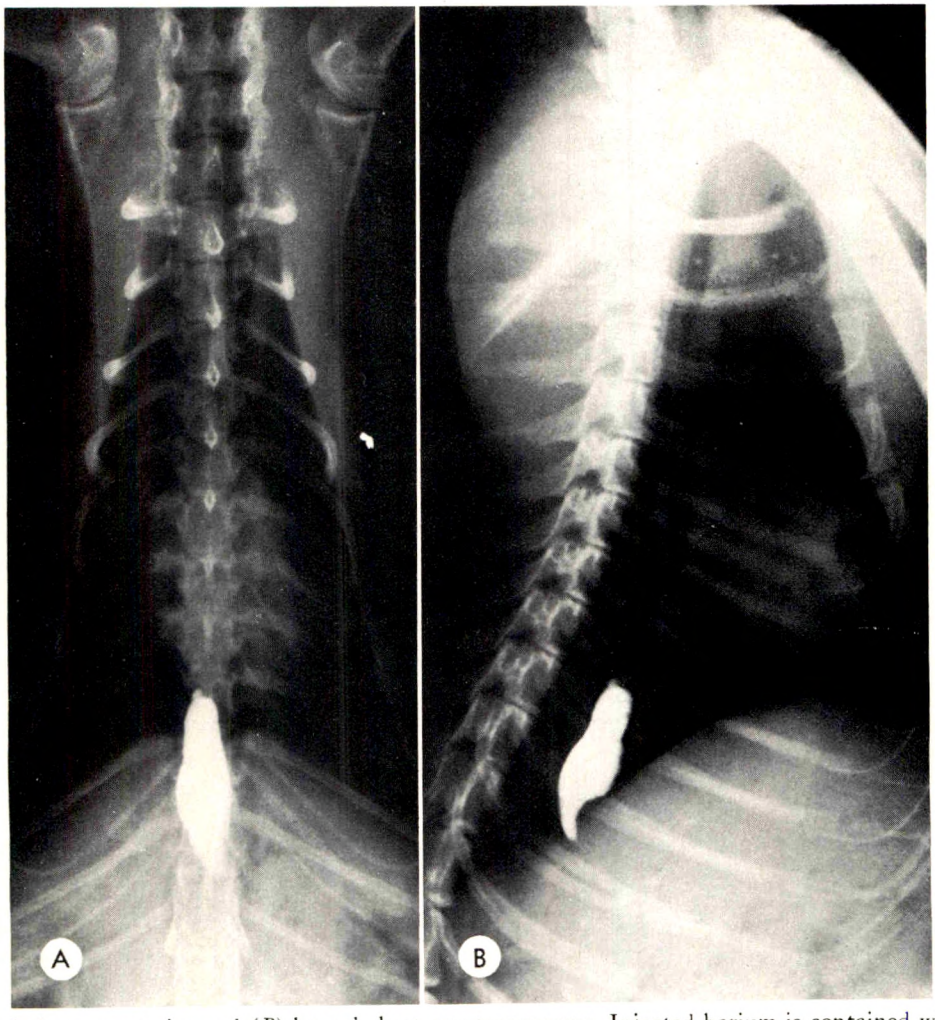

Fig. 2. (*A*) Anteroposterior and (*B*) lateral chest roentgenograms. Injected barium is contained within the mediastinum in animal 3 days after injection.

logic evidence of mediastinitis with minimal attendant clinical signs. Thus, whether or not there were additional deleterious effects of the contrast agents could be assessed. The animals were observed clinically, monitored with serial roentgenograms, and sacrificed at matched time intervals from 2 to 90 days. At necropsy, the mediastinal areas were examined and cultures obtained to identify the organisms. Histologic studies with appropriate staining methods were performed.

c. bacteriologic techniques

Flora was obtained from the upper gastrointestinal tract of humans and cultured for 24 hours in trypticase soy broth with glucose. Subcultures in both aerobic and anaerobic media were used for identification of bacteria. The concentration of the bacterial mixture was adjusted to 10^8 organisms per ml. Before each experiment, 0.5 cc. of the culture broth was mixed with either 0.5 cc. of saline, Gastrografin (aqueous solution of sodium and methylglucamine salts of renografic acid), or commercial barium (Barium Sulphate U.S.P. suspended in carboxy-methylcellulose).

To evaluate whether any bacteriostatic or bacteriocidal effect of the contrast agent was present, a radiometric system for detection and measurement of bacterial

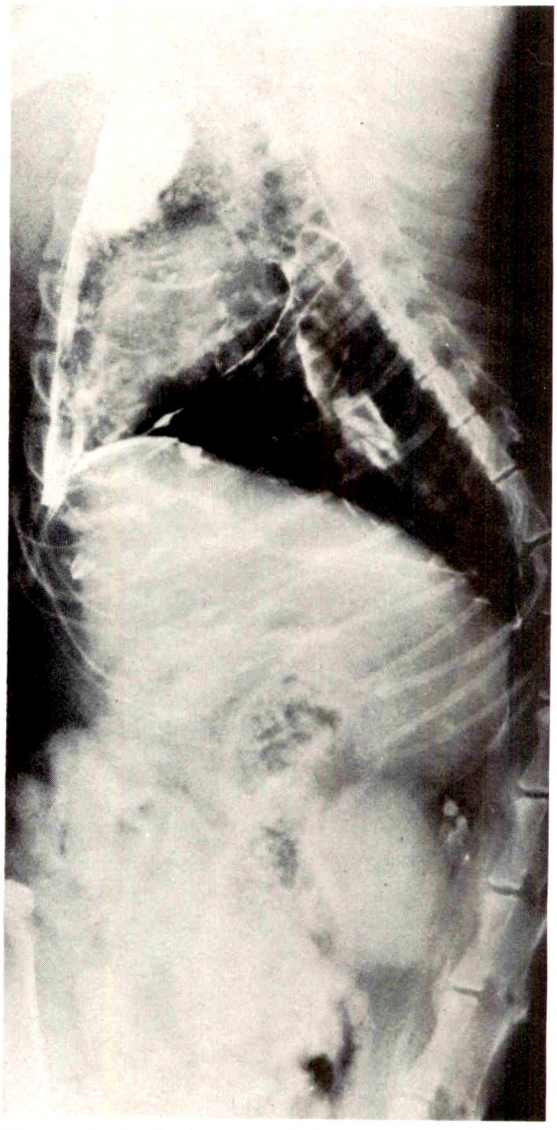

FIG. 3. Lateral chest roentgenogram 8 days after injection of barium. Extravasation of barium has occurred at some time period after 3 days following injection of barium and bacterial flora.

growth (BACTEC)* and pour-plate technique were employed. The details of operation of this system have been published previously and will only be summarized in this communication.

The BACTEC radiometric method is based upon the bacterial metabolism of C^{14} labeled substrates, including C^{14} glucose, C^{14} lysine, and the subsequent evolution of radioactive carbon dioxide as an end product. The released radioactivity is quantified to give an index of bacterial growth and metabolism.

* Bactec 225 Johnson Labs Incorporated, Cockeysville, Md.

TABLE I

NORMAL POOLED HUMAN MOUTH FLORA

1. Coliform and proteus organisms
2. Gram positive aerobic sporeforming bacilli
3. Microaerophilic and anaerobic streptococci
4. Lactobacilli

The major pathways of glucose in bacterial metabolism produce a molecule of carbon dioxide as an end product, which in the BACTEC system is carbon 14 dioxide. Most clinically significant bacteria metabolize glucose to carbon dioxide, at least in small quantities.

The BACTEC system employs an ion chamber for the measurement of radioactivity in order to facilitate the automation of the procedure. A flask containing liquid culture medium, 1.5 microcuries of radioactive substrate, and a magnetic stirring rod are employed. Immediately after inoculation, the flask is incubated at a constant temperature of 37° C. and continuously stirred. The stirring facilitates the release of radioactive carbon dioxide formed by bacterial metabolism from the liquid culture medium into the air above the culture within the flask. Through the use of a circulating pump, the air within the flask is periodically flushed into the ion chamber for quantification of any radioactivity which may be present. Radioactivity produces ionization within the chamber. This is converted to an electrical current that is amplified and measured. The results are automatically recorded on a meter and strip chart for the permanent record.

Human mouth flora (Table 1) was obtained and placed in trypticase soy broth containing glucose. The bacteria were grown for 18 hours. At the time of use there were 10^8 organisms per ml., of which 0.1 cc. was inoculated into the following test substances: 3 Petri dishes containing a sus-

pension of barium in 3 strengths such as dilute (1 to 3); normal (1 to 2); and concentrated (2 to 1). The inoculation was made in the exact center of the barium suspension mixture. At $4\frac{1}{2}$ hours, 0.5 cc. samples were taken at distances of 22 mm. and 44 mm. from the center of the barium suspension. This sampling was repeated at 70 hours and each of the samples was subcultured on chocolate agar and were also placed in the BACTEC system. Additionally, 0.1 cc. of the 10^8 organisms/cc. suspension of normal flora was inoculated into 3 tubes containing varying concentrations of the barium mixture. After 70 hours the bottom of these tubes was broken and 0.5 cc. of this mixture was subcultured on chocolate agar.

RESULTS

All animals tolerated the surgical procedure well. The cats that had only contrast media injected had an uneventful postoperative course (although 1 died of pneumonia unrelated to the contrast medium in the fifth postoperative day). The remainder of the animals drank at approximately 12 hours after operation and began eating the second day. No supportive therapy was necessary. Animals that had bacteria with or without contrast medium injected into the mediastinum started drinking 24–36 hours postoperatively and were given saline subcutaneously to prevent dehydration. After the third day they were clinically normal.

Initially, the distribution of the barium on the roentgenograms was homogenous. Clumping and segmentation of the contrast medium began 3–5 days after injection with and without flora (Fig. 4, *A* and *B*). The rate of resorption of barium was slow and about half of the initial quantity was still visible after 90 days. No detectable opacification of the mediastinal lymph nodes was noted on chest roentgenograms. No barium was seen in the lymph nodes at autopsy. Gastrografin was not visible on roentgenograms obtained the day after injection (Fig. 4, *C* and *D*).

PATHOLOGIC STUDIES

GROUP I—OPERATIVE CONTROLS

In the controls examined after instillation of sterile culture broth, gross and microscopic changes were absent.

GROUP II—COMMERCIAL BARIUM

All 7 cats had well localized white, chalky deposits within the paraesophageal mediastinal tissue at the sites of barium sulphate injection. Three cats[2,3,31] had similar streaks and foci scattered throughout the visceral and intercostal pleura. Histologically, the barium sulphate appeared as yellow-green, refractile, amorphous crystals that were birefringent to polarized light. In lesions occurring 2 and 5 days after barium sulphate instillation, many of the crystals were in both reactive surface mesothelial cells and large macrophages (Fig. 5). In some areas near serosal surfaces, clusters of these crystal-laden cells were under layers of thin, hyperchromatic, mesothelial cells. There were large aggregates of barium filled macrophages within the mediastinum and some were noted in the sinusoids of the regional lymph nodes.

In cats sacrificed 30 days after barium sulphate injection, the serosal membranes contained nodules of crystal-filled macrophages which were surrounded by fibrous connective tissue. Larger masses of these macrophages formed lobules within the mediastinum that were separated by delicate fibrous connective tissue septa (Fig. 6; and 7). The macrophages in some of these lesions appeared spindle shaped and resembled epitheloid cells. Large foreign body giant cells were noted in several cats. Scattered throughout these lobules were mixed inflammatory cells consisting mainly of lymphocytes, a few polymorphonuclear leukocytes, fibroblasts, and small capillaries. The amount of granulomatous inflammation including vascular tissue and fibrosis varied, but was most prominent in animals sacrificed after several weeks.

Bacterial cultures were negative in all cats in this group. The barium sulphate induced lesions were free of bacterial, fungal,

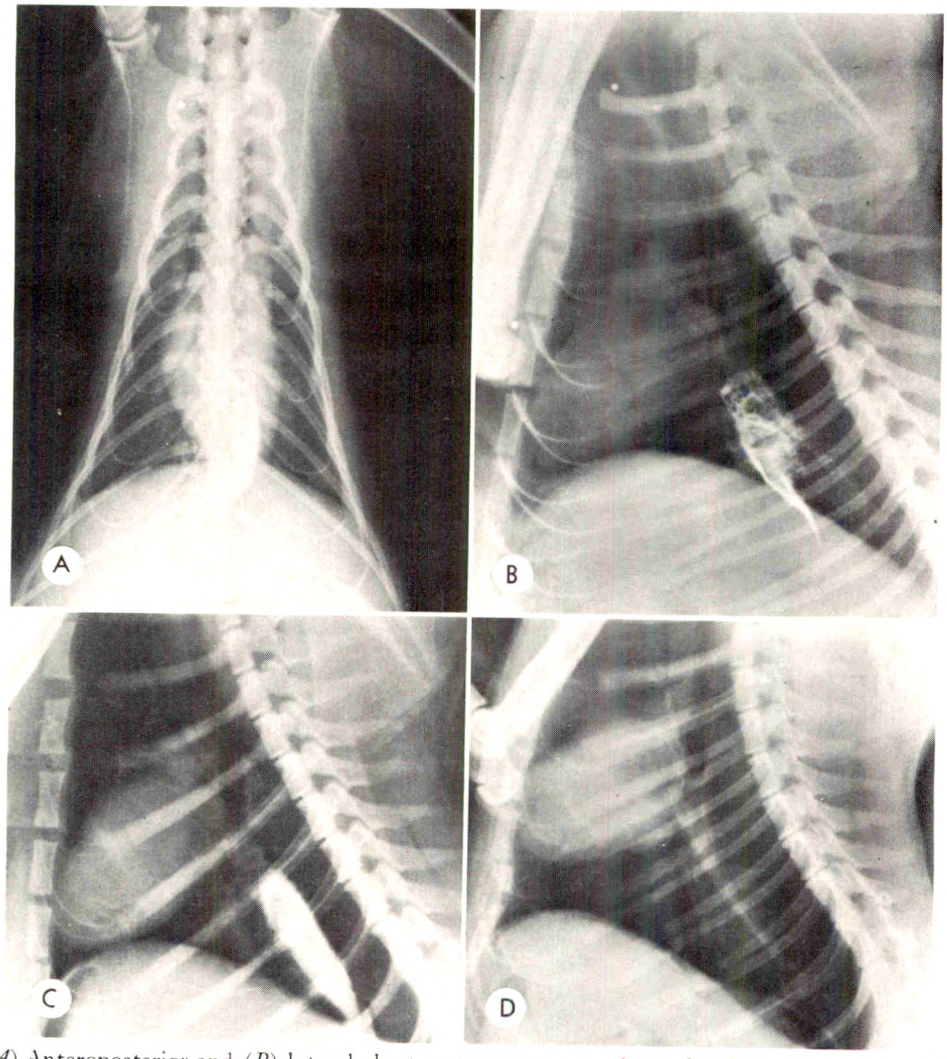

FIG. 4. (*A*) Anteroposterior and (*B*) lateral chest roentgenograms 5 days after barium injection. (*C*) Lateral chest roentgenogram obtained at the time of Gastrografin injection and (*D*) 1 day following injection.

or protozoal organisms by special staining techniques.

GROUP III—STERILE BARIUM SULPHATE U.S.P.

The histologic changes were similar to Group II except that there were fewer polymorphonuclear infiltrates.

GROUP IV—GASTROGRAFIN

The mediastinum and pleural membranes of all 6 cats were free of any residual Gastrografin in animals sacrificed from 3 days to 12 weeks after contrast medium instillation. No pathologic changes were present in the mediastinal sites injected with Gastrografin in 4 of 6 cats. Of the 2 remaining, one had a minimal reaction consisting of a few mixed inflammatory cells 7 days after instillation of the medium; the other had a small hematoma in the wall of the esophagus which was produced traumatically during the surgical procedure.

GROUP V—FLORA

There were no significant gross changes observed in these 4 cats, examined from 5 days to 3 weeks after bacterial inoculation. Histologically, in 2 cats sacrificed after 5 days there was mild to moderate, acute,

mediastinal inflammation characterized mainly by focal and perivascular infiltrates of polymorphonuclear leukocytes (Fig. 8). In 2 cats, sacrificed after 3 weeks, mild to moderate mediastinal reaction with lymphocytes, plasma cells and a few polymorphonuclear leukocytes was present (Fig. 9). *E. coli* was cultured from 1 animal, but was not observed by special stains. The remaining cats were negative for microorganisms by culture and staining methods.

GROUP VI—GASTROGRAFIN + FLORA

There were no gross pathologic changes in any of the 4 cats examined from 7 days to 6 weeks after instillation with this mixture. Histologically, in 3 of 4 cats a mild reaction of mixed inflammatory cells consisting of infiltrates of lymphocytes, plasma cells and a few polymorphonuclear leukocytes was noted in the mediastinal sites 7 days to 2 weeks after mediastinal inoculation. The fourth cat had no inflammation 6 weeks after the procedure.

Cultures and special stains for microorganisms were negative in all of the animals.

GROUP VII—BARIUM + FLORA

The 5 cats in this group were sacrificed from 7 days to 12 weeks after instillation with barium sulphate-bacterial flora mixture. All of these animals had white, chalky deposits both in the inoculated mediastinal sites and scattered elsewhere in visceral and parietal pleura. The microscopic changes were identical to the granulomatous lesions described for Group II in 3/5 cats (Fig. 5; 6; and 7). One animal had extensive fibrous adhesions between the visceral and parietal pleura in areas where contrast medium and bacteria were de-

Fig. 6. Paraesophageal barium granuloma, approximately 30 days after instillation of commercial barium sulphate. Bands of fibrous connective tissue surround and separate the mass into indistinct lobules. The esophageal mucosa is at the bottom. This same change occurred with Barium Sulphate U.S.P., and barium sulphate plus flora. (×10, H and E.)

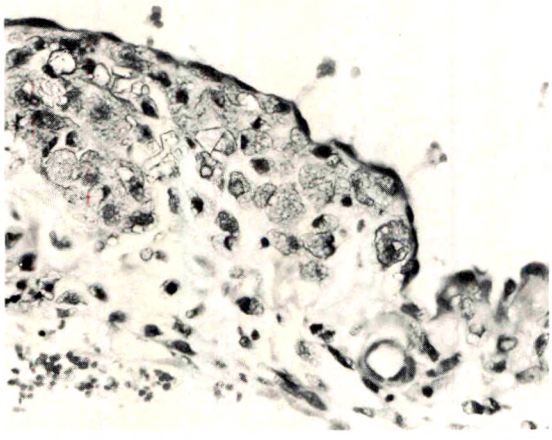

Fig. 5. Early histiocytic reaction to barium sulphate crystals in mediastinal pleura. Many of the crystals are within macrophages. (×500, H and E.)

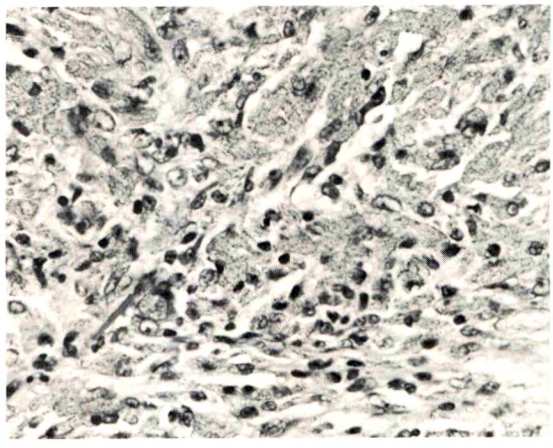

Fig. 7. Magnified area from barium granuloma. The majority of cells are large macrophages containing barium sulphate crystals. Some resemble epithelioid cells. A few mononuclear inflammatory cells are present. (×500, H and E.)

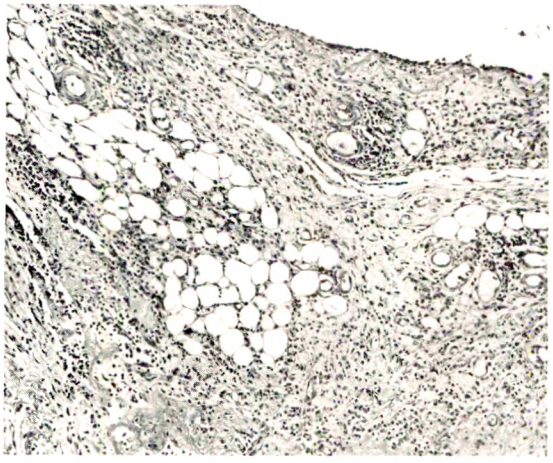

FIG. 8. Mediastinitis produced 5 days after instillation of human flora. Acute inflammatory cells accompanied by some fibrin and edema fluid are within the mediastinal tissues. A suppurative process was not apparent grossly. (×125, H and E.)

posited 12 weeks previously. The other had moderate, acute inflammation associated with barium-induced granulomatous lesions. These abnormalities were noted 12 weeks after instillation of contrast medium and bacterial flora. This animal also had acute bronchitis and patchy areas of acute pneumonia, which were apparently incidental to the experimental procedure. A coagulase negative Staphylococcus was recovered several weeks after the procedure, but was not observed in the stained sections. Cultures and specially stained tissue from the other cats were negative for micro-organisms.

Effect of barium on growth of human flora. The details of the quantitative effects of the contrast media upon bacterial growth will be the subject of another communication, but will be summarized. There was 55 per cent growth inhibition of flora in Barium Sulphate U.S.P. suspension and 70 per cent growth inhibition with commercial barium, as compared with the control in the BACTEC System. No evidence of bacterial growth was present in the samples from the normal and concentrated suspensions of commercial barium in the Petri dishes, or at the bottom of the test tubes containing mixtures of concentrated barium.

DISCUSSION

The natural history, clinical manifestations and prognosis of distal esophageal tears are determined by the location and extent of the perforation.[31,40] Perforations in the lower thoracic esophagus are twice as lethal as those in the cervical portion.[5] The sequence of events following a rent in the lumen of the esophagus is: initially, a chemical inflammation during the first 6 to 8 hours; this is followed by a septic inflammatory response due to aerobic and anaerobic bacterial invasion in the periesophageal region.[34]

More than 70 per cent of untreated patients succumb to septic gangrenous mediastinitis, pleuritis, pyopneumothorax and empyema within several days after the insult.[29] Under a given set of clinical circumstances, the mortality rate increases in proportion to the time interval between perforation and surgical intervention.[5,13,27] Perforation by instrumentation and foreign bodies occurs usually in the cervical esophagus at the level of the cricopharyngeus

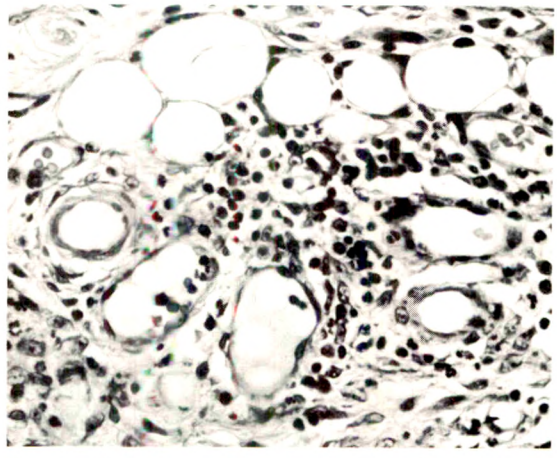

FIG. 9. Resolving subacute mediastinal reaction 2 weeks after instillation of Gastrografin plus flora. Lymphocytes and plasma cells predominate. A similar picture was seen with flora alone after 3 weeks. (×500, H and E.)

muscle, whereas spontaneous perforation invariably affects the lower end of the esophagus.[19,30,38] The diagnosis of esophageal tears or perforation may be made from clinical signs and symptoms or by radiologic examination. Spontaneous rupture of the esophagus exhibits the most dramatic signs and symptoms.[38] Barrett's triad (rapid respiration, abdominal rigidity, and subcutaneous emphysema) and Mackler's triad (vomiting, low thoracic pain, and neck emphysema), are considered to be "characteristic" for the condition.[4,24] In approximately one-third of cases, however, the clinical presentation is atypical and the type of pain may be mistaken for myocardial infarction, dissecting aneurysm of the aorta, perforated ulcer or acute appendicitis.[1,6,23,31] Pain is not a significant feature of perforation in a previously diseased thoracic esophagus.[11] The most important factor in decreasing morbidity and mortality in esophageal rupture or perforation is early diagnosis and immediate surgical intervention.[1,5,6,23,27,29,37,38]

Plain film roentgenograms may be very helpful in the initial diagnosis of esophageal tears, ruptures, and perforations. Air in the planes of the mediastinum or widening of the mediastinal shadow with empyema can be present in longer-standing perforations. Irregularity of the mediastinal air interface is a roentgenographic sign of inflammation and is associated with mediastinitis. However, patients often present with an excellent clinical history for esophageal rent and the chest roentgenogram is negative. If there is a clinical suspicion of persisting esophageal perforation or rupture, contrast examination with fluoroscopic monitoring is imperative.

Experimental studies regarding the tissue reaction to barium sulphate have been largely confined to the peritoneum and lung. Himmelmann[17] in 1933 created an animal model of gastric perforation following barium instillation. He believed that stomach contents with barium were more deleterious to the peritoneal cavity than gastric contents alone. Thomas[36] deposited barium sulphate in the peritoneal cavity of dogs and found that barium particles were initially distributed in a uniform fashion over the abdomen. After several hours these particles were agglutinated on the omentum. The cellular reaction was fibroblastic in type leading to granuloma formation. Adhesive fibrous changes were minimal. The temporal sequence of tissue reaction of the peritoneum of dogs to barium sulphate was reported by Kleinsasser and Warshaw;[21] the typical pathologic finding in the peritoneal cavity was a barium granuloma. These authors concluded that moderate amounts of barium were not likely to produce intestinal adhesions. Kay and Choy[20] found that the basic response following intraperitoneal injection of large doses of sterile barium in mice was a histiocytic type of granuloma. This abnormality was noted after the fourth day and was followed by loose fibrous adhesions accompanied by bowel distention. Sanders and Kobernick[33] implanted barium in the retroperitoneum of rabbits and observed tissue reactions similar to those described by previous authors. They found, however, that barium without significant infection was not harmful and caused only local reactions.

Cochran and co-workers[10] in a comparative study of the effects of barium sulphate preparations concluded that commercial barium was more deleterious in the peritoneal cavity of dogs than pure barium sulphate. They state that the hazards of fecal intraperitoneal spillage are due to infection, but contend that the combination of barium and feces was more harmful than either alone. Sisel *et al.*[35] found a lower survival rate in experimental colonic rupture of rabbits followed by an enema utilizing barium sulphate as compared with saline or water soluble contrast medium. Zheutlin *et al.*[41] found a 51 per cent mortality rate due to spillage of feces and barium into the peritoneal cavity as a complication of barium enema. Others[16] have stated that im-

mediate laparotomy is mandatory with free barium sulphate in the peritoneal cavity and extraperitoneal leakage of barium is associated with less morbidity than intraperitoneal leakage.

In the lung it has been shown that the tissue reaction depends upon the length of time that barium is present. Immediate inflammatory reaction develops initially followed by granuloma formation. The lung parenchyma will revert to normal after 4 months with no evidence of fibrosis. In the presence of a communication of the tracheobronchial tree with the pleural cavity, barium is either coughed up or can be removed by chest tube and irrigation.[18] The studies of Christoforidis *et al.*,[9] Andrews,[3] Reich,[32] and French[12] revealed that barium sulphate, when used in moderate amounts, is less hazardous in the tracheobronchial tree than water soluble iodinated contrast media. Apart from transient mechanical blockage, barium does not produce any acute inflammatory response.

As we have previously stated, experimental studies of the effect of contrast media in the mediastinum have not been reported, but clinical impressions and implications abound in the literature.[2,6,15] A number of authors believe that radiographic contrast produced by barium is superior to the iodinated contrast material in the diagnosis of the esophageal perforation.[2,15]

From the foregoing discussion it may be concluded that there are differences of opinion regarding the suitability of barium as a contrast medium in suspected perforations. However, it is generally assumed that barium has an additive deleterious effect in all cases of a suspected perforated viscus. Again, this impression appears to be based on casual observations and extrapolation from experiments in the abdominal peritoneum. We could find no data with regard to the effects of contrast media in the mediastinum. Although we felt that the experience from the peritoneal cavity was important, the character of the tissue response might be entirely different in the mediastinum.

Our experiments were designed to create a model in which the effect of barium in the mediastinum could be assessed and compared with the most commonly employed water soluble contrast medium. From our results, barium does appear to cause granuloma which was not seen with Gastrografin. However, it does not seem to have an additive deleterious effect, when mixed with bacterial flora. The granuloma formation is a localized phenomenon and could be largely avoided if the barium were removed at time of surgery.[15] Pathologically, the animals with the combination of flora and barium initially could not be separated from those with flora (except for the $BaSO_4$ granules) or in the later phases (after 7–10 days) from barium sulphate alone. These pathologic observations were made from review of the slides without knowledge of the experimental group or clinical history.

The lack of significant histologic reaction to Gastrografin was expected from previous studies in other anatomic areas. It appeared to be rapidly absorbed and removed from the mediastinal area. No change in bacterial growth or colony movement was observed with this water soluble contrast medium.

Serial sacrifice of the animals from 2 to 90 days provided information regarding the progression of the lesions. However, a larger animal population for each time period would have provided a more accurate assessment of the spectrum of pathologic changes and diminished the effect of unrelated pneumonias. Severe clinical mediastinitis could be produced by inoculation of a concentrated mixture of the human flora, but this mixture resulted in death of such a large percentage of the animals that, in order to grade the histologic and clinical reaction, a dilute solution was utilized. The mediastinitis thus produced was not clinically dramatic, but histologically readily apparent. We felt

that this would enable us to determine if any added deleterious effect was due to the combination of contrast media and flora. Thus, extension of this study should include a much larger animal population in which more animals could be sacrificed at shorter time intervals (especially in the first 48 hours following injection). Serial concentrations of the flora should also be utilized.

The results obtained in the second part of the study show that barium has an inhibitory effect on the growth of bacteria, which is more pronounced when pure Barium Sulphate U.S.P. is used. The absence of growth in subcultures of the samples taken from Petri dishes and test tubes is presumably due to physical factors preventing the spread of bacteria in concentrated barium. It appears that barium agglomerates in tissue are more likely to remain as sterile masses rather than as sources of infection.

The effect of the barium on bacterial growth and colony movement was not totally unexpected, but its extent would not have been predicted. The major etiologic component of the barium effect is felt to be mechanical. Heavy particles of any type when present in a bacterial suspension will limit growth. Barium probably does not have a bacteriocidal effect in the concentrations employed clinically, until it is localized or concentrated by some active process after its introduction into the gastrointestinal tract. Roentgenograms were utilized to insure that the contrast medium was initially placed in the mediastinum and that spillage into the pleural cavity occurred later. The temporal sequences of the appearance of "free" barium suggested that its extravasation was most probably due to infection and not to the instrumentation at the time of surgery. The chest roentgenograms did reveal several instances in which barium was seen in the pleural space. However, the characteristic findings of mediastinitis were not present. No definite widening or irregularity of the mediastinum was seen in any of the combinations reported herein. In the animals in which the concentrated flora was injected, pneumonias and other abnormalities were present on the chest roentgenograms.

These observations are obviously preliminary and extension of this type of study will be necessary before definitive statements regarding the various choices of contrast media can be made. Barium sulphate is, because of its physical properties, an excellent diagnostic contrast medium. For the location and evaluation of the site and extent of esophageal perforation, it is superior to the iodinated contrast media. In the light of the results obtained from this experimental study, we believe that augmentation of the mediastinal inflammatory response by barium in the presence of bacterial contamination is probably less than currently assumed. As a practical compromise in patients with suspected rupture or perforation of the distal esophagus, we first obtain a limited upper gastrointestinal series with a water soluble contrast agent. If this initial study is negative, it is repeated utilizing barium as the contrast medium.

SUMMARY

In order to study the effects of the commonly employed contrast media in the mediastinum, various combinations of contrast media and flora were instilled in the mediastinum of 30 domestic cats.

The animals were sacrificed at serial time intervals following the mediastinal injection.

These data suggest that the water soluble contrast media cause no significant histologic reaction.

Barium causes granuloma formation, but has no additional deleterious effect when mixed with normal human mouth bacterial flora of various concentrations. Because of its superior physical properties, it appears to be the contrast agent of choice

in difficult clinical problems with regard to esophageal rupture or perforation.

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ENTEROGENOUS CYST OF THE COLON PRESENTING AS A RETROPERITONEAL TUMOR IN AN ADULT*

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ENTEROGENOUS cysts, enterocystomas or duplications of the alimentary canal are a group of congenital abnormalities characterized by cystic or tubular formations connected with or adherent to any segment of the alimentary canal. The diagnosis of these cysts is not uncommon in the pediatric age group, but is rather infrequent in the adult age group.

In a review of the literature conducted in 1961 by Anderson *et al.*,[1] of the 63 cases collected, the esophagus was involved in 26, the stomach in 9, the duodenum in 6, the small intestine in 10, and the colon in 5. Both the esophagus and the stomach were involved in 3 cases, the small and large intestine in 2, and in 2 cases multiple lesions were present.

Our survey of the literature revealed 21 additional cases of duplication of the colon—a few not reported by Anderson *et al.*[1]—and are tabulated in Table 1.

REPORT OF A CASE

H.L. (Q.H.C. No. 15-11-82), a 57 year old female, known diabetic under good control, was admitted because of discomfort—and at times moderate to severe pain—in the right lower quadrant of the abdomen of several weeks' duration. The past history was noncontributory apart from appendectomy 9 years prior to admission. The physical examination showed a normally developed woman in no apparent discomfort. An abdominal scar was noted in the right lower quadrant of the abdomen. On palpation of the abdomen there was no tenderness, or spasm. A firm, fixed mass was felt in the right flank, extending to the lower quadrant and measuring roughly 8×10 cm. in diameter. Rectal and vaginal examinations were unmarkable and laboratory studies of the uri and blood were within the normal limits.

Roentgenograms of the chest showed no s nificant lung changes. A standard roentgen gram of the abdomen demonstrated a la lobulated mass on the right, extending from t 12th rib to the middle third of the iliac bo A thin rim of calcium deposit was noted alc the superior and medial contours of the ma The right kidney was displaced medially a separated by clear interface from the upp border of the mass (Fig. 1). Intravenous exc tory urography demonstrated normal conc tration and excretion bilaterally. The rig

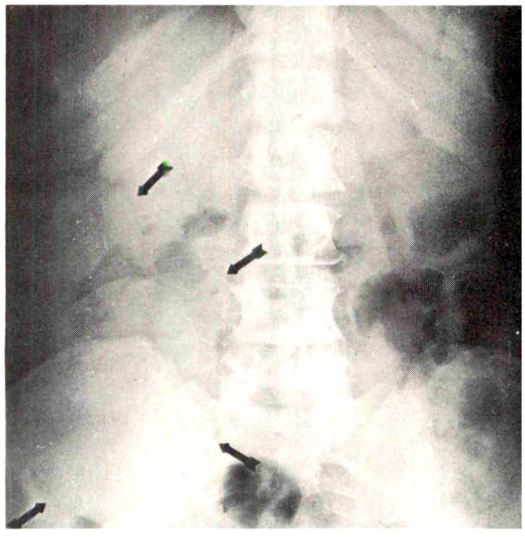

FIG. 1. Standard roentgenogram of the abdon demonstrating on the right hemi-quadrant a la cystic mass, apparently lobulated, reaching fr the 12th rib to the lower third of the iliac bone a medially, almost to the midline. The right kidn separated from the mass by a clear interface displaced medially.

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kidney was displaced medially and appeared somewhat rotated in its transverse diameter. The impression was that the mass, or masses, did not originate from the kidney. A barium enema examination did not reveal any intrinsic organic lesion; however, the cecum and ascending colon were displaced anteriorly and slightly medially (Fig. 2; and 3). On fluoroscopic examination it was noted that there was an intimate relationship between the ascending colon-cecum and the mass which appeared to be located in the retroperitoneal space. An upper gastrointestinal tract examination with small bowel series showed displacement of the second portion of the duodenum with large smooth concavity in the middle and lower third of its lateral aspect, with associated displacement of the small intestine and a pressure effect on the ascending colon (Fig. 4). The roentgen findings indicated the presence of a large mass with interrupted calcific rim, originating from the retroperitoneal space. The differential diagnoses included the possibility of a neoplastic lesion, lymphosarcoma, a duplication of the colon and an abnormally located ovarian tumor. In order to reach a more definite roentgenologic conclusion, arteriography of the superior and inferior mesenteric arteries was performed. This demonstrated the presence of an avascular mass in the right quadrant of the abdomen (Fig. 5).

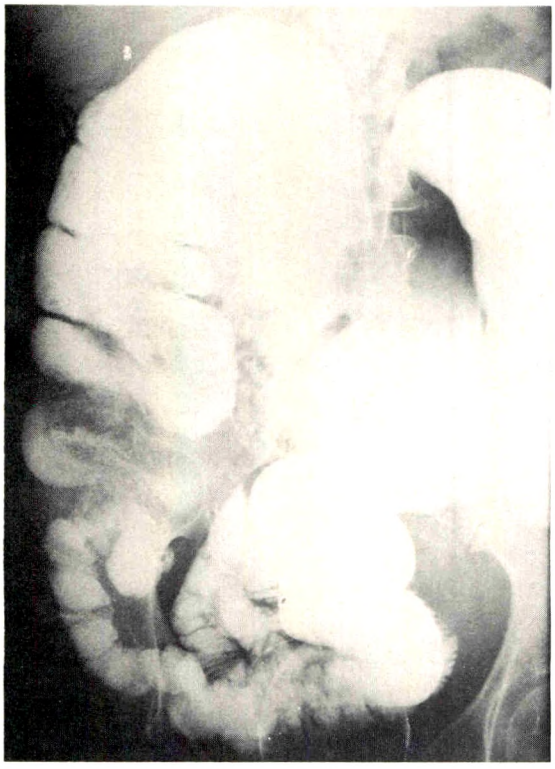

Fig. 2. Pressure effect in the ascending colon and cecum produced by the mass located posteriorly. There is no evidence of intrinsic lesion in these segments of colon. A slight flattening is noted in one segment of the distal ileum, facing the cecum.

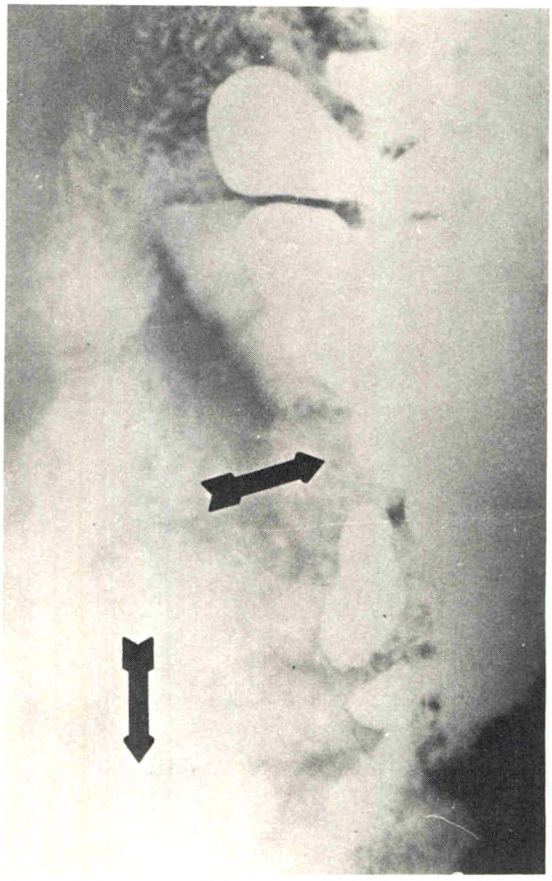

Fig. 3. Lateral projection during the barium enema examination showing the smooth wide pressure effect on the proximal ascending colon and cecum, displaced anteriorly, and on segments of the distal ileum, displaced downward.

An exploratory laparotomy was performed. The right colon and cecum were displaced by a large cystic mass that filled the entire retroperitoneal space on the right side and extended upward to the level of the 12th rib posteriorly. The mass was firmly adherent to the cecum and the ascending colon, but free from other adjacent structures. No other abnormalities were noted in the abdomen. An attempt was made to dissect the right colon from this mass, but it

TABLE I

ENTEROGENOUS CYSTS OF THE COLON

Author	Sex	Age	Main Symptoms	Roentgen Findings	Surgical and Pathologic Findings
Theis[26]	M	26	Recent, gradual onset of abdominal pain and constipation.	Mass impinging into cecum.	Cystic mass adjacent to the ileocecal valve. Enteric duplication.
Weber and Dixon[27]	F	27	Repeated attacks of sharp pain across lower abdomen. Other abnormalities were present: double uterus and cervix, and agenesis of the right kidney.	Duplication of colon.	Operated at 3 years of age for intestinal obstruction. At age of 19 symptoms of acute appendicitis developed. At operation 2 appendices were demonstrated and what was thought to be a mesenteric cyst was drained. A colon duplication was removed in 2 stages at a later date.
Martini[13]	M	31	Discomfort in the right lower quadrant for at least 1 year. The pain became very severe and the patient was admitted with the diagnosis of acute appendicitis.		A cystic mass was found in the pericecal area and was removed. No acute appendicitis was present. The histologic diagnosis was enterogenous cyst.
Kraft[8]*	F	34	History of intractable diarrhea. Sigmoidoscopy showed inflammation of posterior rectum, just within the anal verge.	Fixation of sigmoid colon to the rectum.	An inflammatory cystic mass, elongated in the longitudinal axis of the rectum, was removed and proved to be a rectal duplication.
Martorell and Murphey[14]	F	30	Six weeks after childbirth the patient noted a "bearing down" sensation in the rectum. A retrorectal mass was found on palpation and aspirated, but reappeared.		A cystic mass 6×5×3 cm. was found intimately adherent to the submucosa of the rectal wall. The histologic report was congenital duplication of the rectum.
Martorell and Murphey[14]	F	37	At age 33, seven weeks postpartum, a cystic mass was felt between the rectum and the sacrum.		Cystic mass found within the rectal wall. The pathologic report was of infected enterogenous cyst of the rectum.
Martorell and Murphey[14]	F	37	A tumor behind the rectum was found on routine examination.		A multilocular cyst was removed from the posterior wall of the rectum and proved to be an enterogenous cyst of the rectum.
Montanez[19]	F	48	At time of hysterectomy a tumor mass was noted in the sigmoid colon. Sigmoidoscopy performed later showed only sharp angulation of sigmoid.	Barium enema examination showed the sigmoid to be displaced superiorly and medially by an extrinsic mass, thought to be a colon duplication.	Surgery was refused.
Larizadeh and Powell[11]	F	44	Pain in the right lower quadrant of the abdomen, associated with nausea and backache.	Barium enema examination showed a tubular formation along the ascending colon.	Colon duplication with a carcinomatous growth in the blind end of the duplication.
Krajčovič *et al.*[9]	F	45	The patient had previous surgery for a double uterus.	Intravenous excretory urography demonstrated an agenesis of the left kidney and ureter, and a barium enema study demonstrated a double descending colon.	Duplication of the descending colon. A left hemicolectomy was performed.
Breen and Weinberg[2]	F	20	A double vulva was noted since birth. A double vagina, 2 urethras and rectums were demonstrated at time of delivery of first child. A uterus didelphys was also noted after delivery.	Excretory urography showed 2 bladders, and a barium enema examination revealed a complete duplication of the colon.	Surgical intervention was deferred.

* The author mentions 70 cases of rectal duplication previously reported.

TABLE 1 (*Contined*)

Author	Sex	Age	Main Symptoms	Roentgen Findings	Surgical and Pathologic Findings
Rodriguez *et al.*[23]	M	40	History of constipation. Palpable mass in midabdomen.		At surgery duplication of the colon was found.
McCready *et al.*[17]	F	19	No symptoms related to the gastrointestinal tract. On a routine pelvic examination soft pelvic mass was noted.	Barium enema examination showed the rectal ampulla to be displaced to the right, and a large tubular filling defect in the sigmoid communicating with its lumen.	A short duplication of about 10 inches was removed at surgery and the histologic report was of congenital duplication of the colon.
Campbell and Wolff[4] (Case 3)	F	27	A perirectal abscess developed after the birth of the first child. During the ensuing years recurrent perirectal abscesses required incision and drainage. Finally the patient was admitted with an acutely inflamed retrorectal abscess draining pus from the rectum.	A fistulography was performed through the fistulous tract in the rectum and demonstrated a pouch behind the rectum, separated from the inflamed cyst.	The inflamed pouch was removed and 1 year later a 2 cm. cyst was excised from the posterior wall of the rectum. Congenital duplication was the histologic diagnosis.
Heiberg *et al.*[6]	F	50	The patient was admitted to the hospital because of sharp abdominal pain, vomiting and diarrhea. A 5×10×15 cm. tender and mobile mass was palpable on the right side of the abdomen.		At surgery a perforated cecal mass was found and a right hemicolectomy was performed. The pathologic report reads in part: "at the level of the ileocecal valve but situated posteriorly a mass 6×8 cm. is demonstrated containing thick brownish material." The histologic diagnosis was of adenocarcinoma in a colonic duplication.
Mazier and Ferguson[15]	M	31	History of chronic constipation, crampy pain and diarrhea.	Suggestion of megacolon. A diagnosis of Hirschsprung's disease was made by rectal biopsy.	Colostomy and removal of a Meckel's diverticulum were performed as the first stage. At the time of the second operation, a colon duplication was found and confirmed by histologic studies of the specimen.
Tamoney and Testa[24]	F	61	Repeated abdominal crampy pain with nausea for past 4 weeks. Large tender mass in the right lower quadrant.	Duplication of the proximal ascending colon was demonstrated with a mass arising from its cul-de-sac.	Duplication of the ascending colon with a villous adenoma arising from its cul-de-sac and showing areas of a well differentiated adenocarcinoma.
Reilly *et al.*[22]	F	63	Pain in the left side of abdomen; mass present on palpation.	Lesion in the mid-descending colon partially obstructing the lumen.	At surgery a 5×3 cm. cystic mass was found to run parallel to the mid-descending colon and was removed. The histologic diagnosis was of colon duplication.
Mezzetti and Bresciani[18]	F	19	Patient admitted to hospital with diagnosis of acute appendicitis.		A cystic mass attached to the cecum was found and was removed with difficulty. The diagnosis of enterogenous cyst was made histologically.
Reid[21]	M	20	Intermittent colicky abdominal pain for 2 weeks.		Mass 15 cm. in diameter, adherent to the descending colon, and perforated, communicating with a wide opening with the lumen of the colon. Histologic report was duplication of the descending colon, perforated.
Kučišec and Rudan[10]	M	23	Chronic constipation. At age 5½ under the assumption that he had Hirschsprung's disease, splanchnictomy and left gangliectomy were performed. Later the presacral plexus and ganglion of the inferior mesenterium were removed, but the patient remained chronically constipated.	Barium enema examination showed markedly distended colon with redundancy of the sigmoid.	Removal of 20 cm. of sigmoid. Duplication of colon.

FIG. 4. Marked pressure effect with displacement produced by the cystic mass on the ascending colon. Clearly demonstrated is the calcific rim along the upper and lower contours of the mass.

was impossible to establish a plane of cleavage. In an attempt to free the cyst from the colon, the cyst was ruptured and a jelly-like material extruded. The cyst was then completely evacuated and resected together with the right colon and the terminal ileum. A primary end-to-end ileo-transverse colostomy was performed.

The pathologic report reads, in part, as follows: the surgical specimen consisted of the resected portion of the terminal ileum, cecum and ascending colon together with a large collapsed cyst measuring 12×12×10 cm. (Fig. 6), located in the angle between the ileum and ascending colon and adherent to the serosal aspect of these organs. When fully opened, the cyst was seen to be unilocular and contained residual gelatinous straw colored material. Portions of its walls were thickened and calcified. There was no communication with the lumen of the colon. In the cecum cul-de-sac there was a mucosal ulceration measuring 2×1.5 cm. associated with considerable thickening of the wall.

Microscopic studies revealed the walls of the cyst to be predominantly fibrotic with areas of atrophic smooth muscle bundles. Of note was the consistent presence of a layer of nerve bundles and some ganglia situated appro mately halfway throughout the thickness of t wall. This would correspond with residual n enteric plexus of Auerbach (Fig. 7). There we also signs of chronic active inflammation. one area where the muscularis was better p served, this merged with the muscularis of t colon forming a common septum (Fig. 8). T mucosa was denuded except for a focal zo where markedly hyperplastic mucin-secreti columnar epithelium was present. Althou fibrotic, all the constituents of the intesti wall were represented in the cyst, which w considered to be an enterogenous cyst. Sectic of the cecal ulceration showed well vascular granulation tissue and marked submuco fibrosis, consistent with ischemic typhli (Fig. 9). This was secondary to a marked c literative endarteritis in sizable vessels locat within the fat adjacent to the cyst wall a was probably a consequence of the pressu effects by the large mass on the adjacent arter walls.

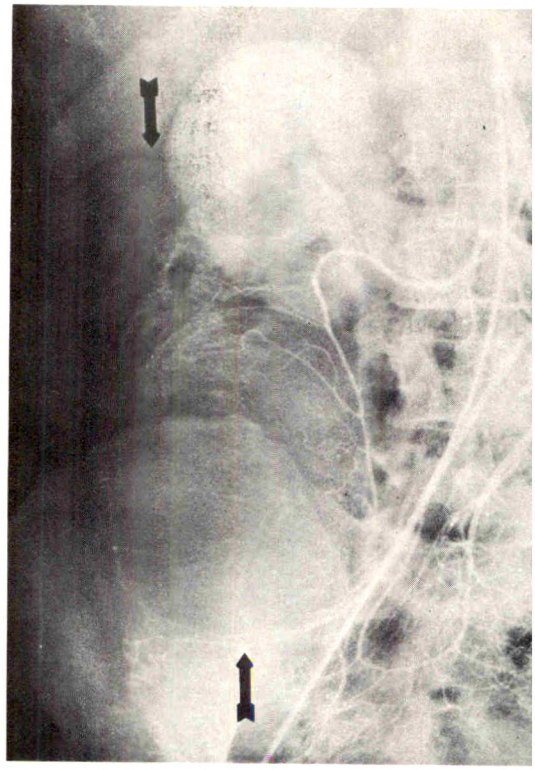

FIG. 5. Angiogram demonstrates normal arteri which are displaced by an avascular mass and su round it.

DISCUSSION

Enteric duplications may occur in the intermuscular, submucosal or subserosal layers of the intestinal wall. In the latter event, the cystic formation may detach itself from the intestinal wall and lie adjacent to its point of origin. Histologically, the walls of the cystic or tubular formation resemble that of the intestine and consist of mucosa, submucosa and muscular layer. It should be noted, however, that the epithelial lining may be quite altered because of associated phenomena, such as pressure and inflammation, as noted in our case.

Several theories have been postulated on the etiopathogenesis of enteric duplication. In 1907, Lewis and Thyng[12] suggested that enterogenous cysts derive from diverticula which appear along the alimentary canal of the embryo in the fourth to the eighth week of age, and later regress completely. If one of these pouches does not disappear, it may result in a duplication of a segment of the alimentary canal.

In 1934, Hughes-Jones[7] conducted a series of studies on the intestines of human embryos in order to demonstrate the pos-

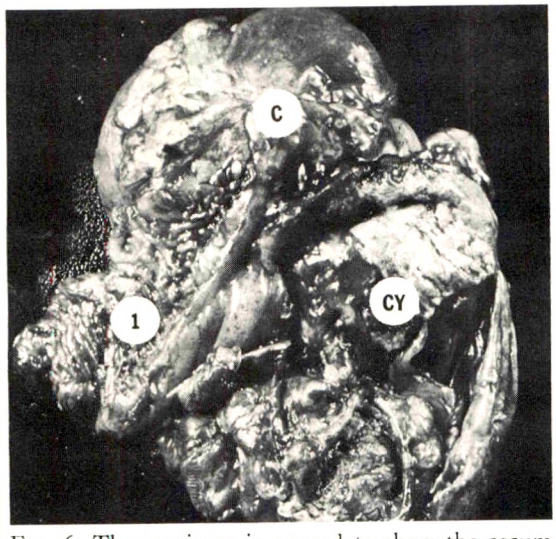

Fig. 6. The specimen is opened to show the cecum (C), ileum (I), and the cyst (CY), after removal of the residual gelatinous material.

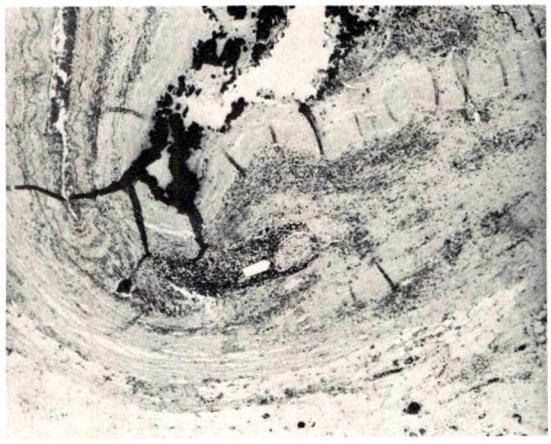

Fig. 7. Demonstrated is the wall of the cyst consisting mostly of concentric fibrous tissue lined by mucinous and calcified debris. Approximately halfway through the thickness of the wall is a layer of nerve bundles (residual Auerbach's plexus), with adjacent lymphocytes. One nerve bundle (white arrow) is seen in the center of the field (H. & E. ×25).

Fig. 8. Common septum showing markedly hypoplastic mucosa and subjacent muscularis (H. & E. ×100).

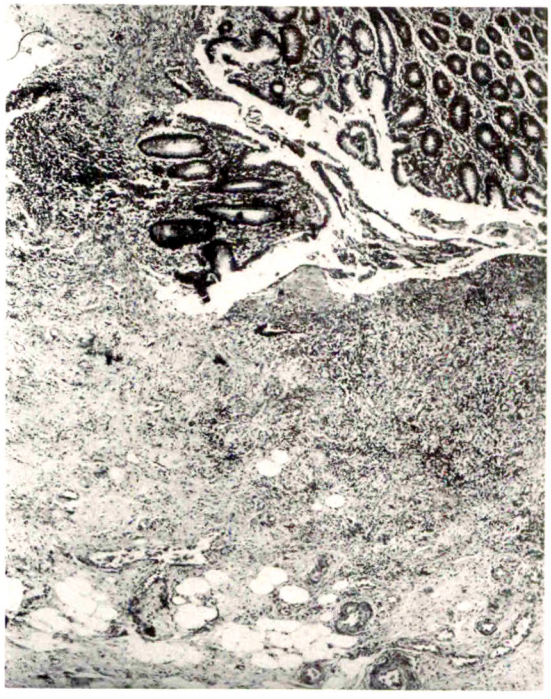

FIG. 9. Wall of cecum showing ischemic cecitis with ulceration and subjacent markedly hyperplastic granulation tissue interrupting the muscularis (H. & E. ×100).

sible cause of enterogenous cysts. He found definite evidence, in the segments of intestine involved, of epithelial sequestrations and felt that "such observations prove nothing, but they demonstrate the possible source of origin of enterogenous cysts." This process of sequestration of buds of intestinal epithelium would occur in the submucosa before the embryo reached the 23 mm. stage.

Bremer[3] postulated that around the sixth week of intrauterine life, the sudden rapid growth in length of the intestinal tract is preceded by an increase of its epithelial cells to such an extent that in certain regions, the lumen of the tubes becomes so much reduced or even occluded. "Normally the cells of the thickened epithelial mass secrete fluid that gathers into small intercellular droplets, called vacuoles. These are usually arranged in chains or rows lengthwise of the tube and, with individual expansion, may coalesce with each other or with the main lumen." In rare cases the chains of fused vacuoles may retain their form and cause intestinal duplication (Fig. 10).

Veeneklaas[26] observed the association of enteric duplication with spinal abnormalities and advanced a notochordal theory for the pathogenesis of gastrogenic cysts of the mediastinum. During the third week of embryonic life, a neuroenteric canal exists between the dorsal ectodermal plates and the endoderm situated at the level of the second thoracic vertebra. Any abnormal differentiation at this stage of development could result in anomalies of the intestine or spine, and at times of both.

In 1953, Ravitch[20] stated that duplication of the colon, of the genitourinary tract and the various doubling of the lumbosacral segments of the spine could be explained as partial twinning. He implied that complete duplication of 1 or even 2 systems could be the result of a perfect

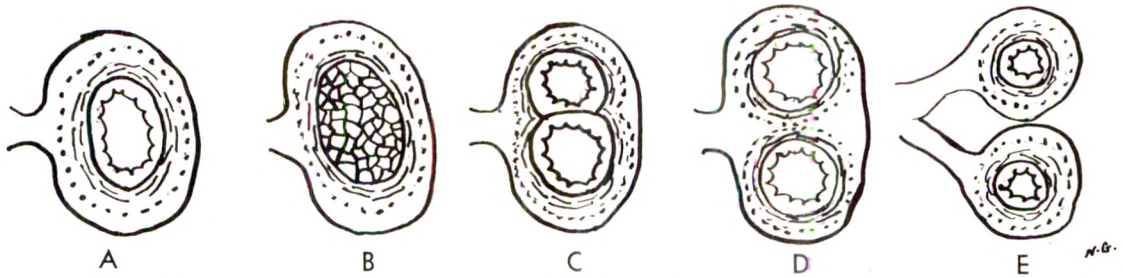

FIG. 10. Diagrammatic representation of the formation of an enterogenous cyst: (A) early stage; (B) solid stage; (C) appearance of 2 vacuoles in the cell mass; (D) 2 epithelial lumens with circular muscle in between; and (E) appearance of duplication with its complete intestinal wall and a separate mesentery. (Modified from Bremer.[3])

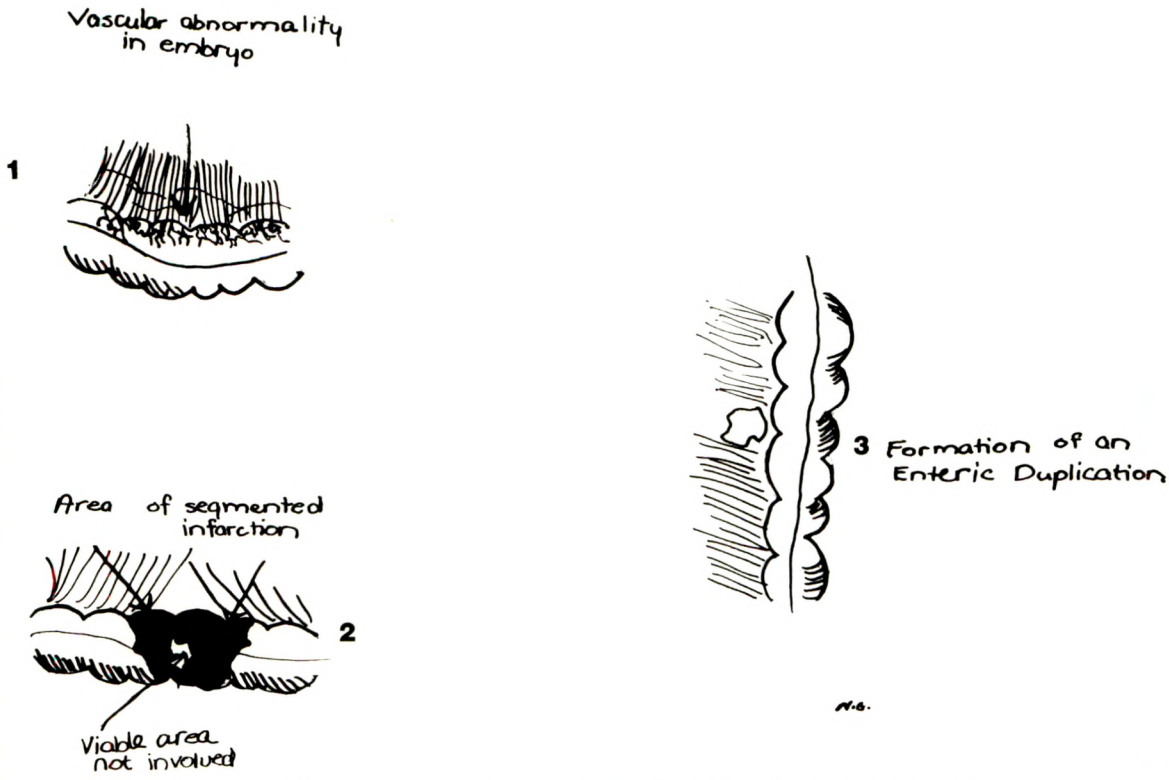

Fig. 11. "Vascular occlusive" stages in the formation of enterogenous cyst. (Modified from Favara *et al.*[5])

doubling of the caudal end of the embryo, most likely within the first 2 weeks of embryonic life.

McLetchie *et al.*,[16] in 1954, suggested that adhesions could occur between the neural canal and the entoderm, resulting in traction on the entoderm with secondary pinching off of cells and later on formation of an enteric duplication.

More recently, Favara and his associates[5] presented a vascular theory. In an analysis of 39 duplications found in 37 patients of neonatal age, it was felt that duplications of the small intestine were the result of an ischemic insult to the small intestine occurring in the intrauterine life. A mesenteric vascular occlusion and segmental bowel infarction occurring in a sterile environment would result in a reabsorption of the infarcted segment of bowel and mesentery. A fragment of intestine not involved in the process of necrosis would be nourished by vessels originating from adjacent inflammatory tissues. "This intestinal remnant, in a sterile environment, survives and develops gross and microscopic features of a typical cystic enteric duplication" (Fig. 11).

The roentgen findings of duplication of the colon vary in accordance with the type of abnormality involving the large bowel (Fig. 12). The duplication may extend through the entire length of the colon presenting a double terminal ileum down to a double rectum, or it may be limited only to a segment of the colon with openings proximally and distally, or with only 1 opening. However, at times the duplication has no communication with the large intestine and would appear as a mass usually adherent or adjacent to the cecum and ascending colon, more rarely to the descending colon and rectum (Table 1). At times other abnormalities can be associated, such as

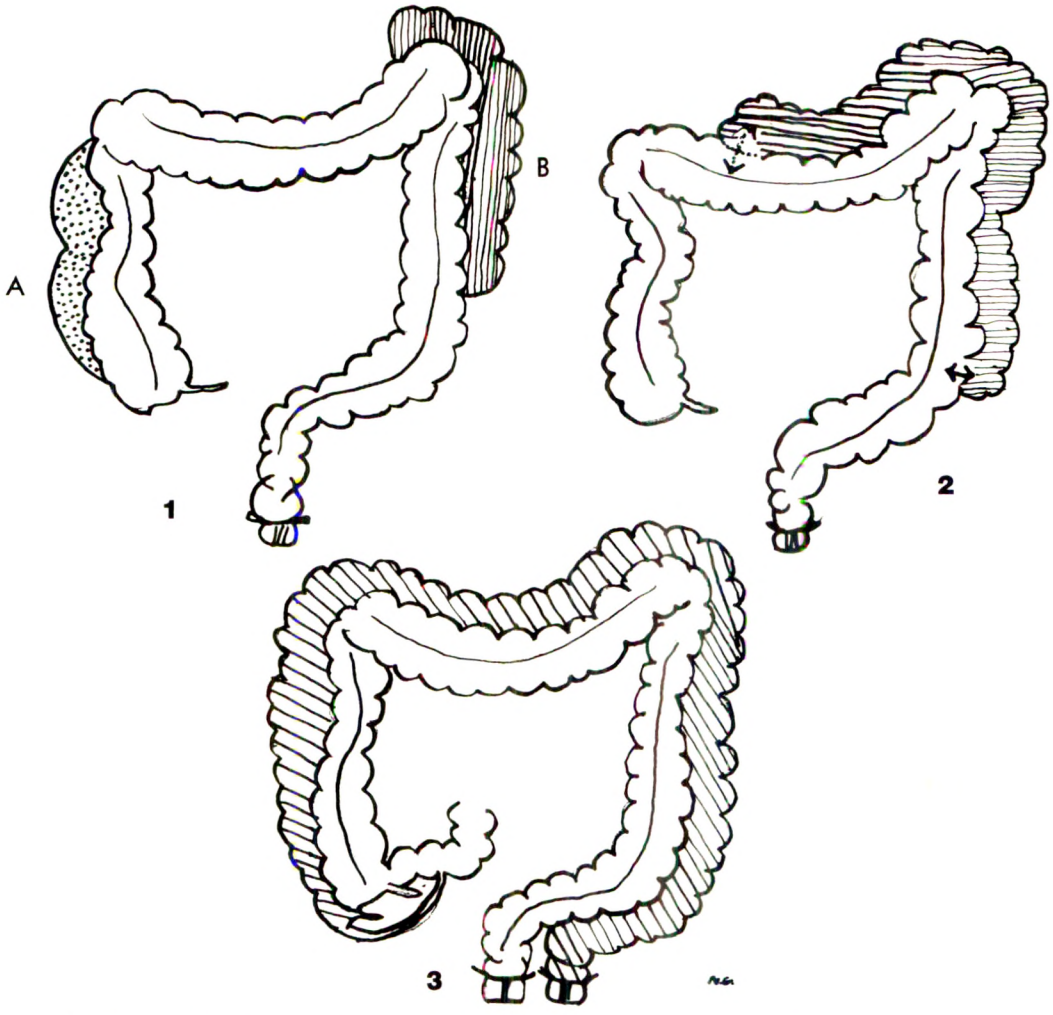

FIG. 12. Diagrammatic representation of most common hindgut duplications: (1, A) cystic, (1, B) tubular without communication with the colon; or (2) communicating with the lumen, either at both ends or only at one end; and (3) complete hindgut duplication with 2 terminal ileal coils, appendices and 2 recti and ani.

double uterus and cervix, or double bladder or abnormalities of the vertebral column.

The symptomatology and clinical findings are related to the type and location of the duplication. In reviewing the literature, the symptoms presented by the cases reported varied from vague abdominal discomfort lasting a very short time or months, to an acute and severe abdominal pain necessitating an emergency surgical intervention. The diagnosis is usually established at surgery and confirmed by microscopic study of the specimen.

In the review of adult cases by Anderson *et al.*[1] and of the other cases found in the literature, the ages ranged between 14 and 68 years, and 16 of the 84 cases reviewed were 50 years of age or older. Anderson and his associates[1] noted a sex ratio of 2 to 1 for the male sex, but in our series there were 17 females (including our case) and 6 males. Finally, we feel that it is important to mention that in 3 cases an adenocarcinoma was found in the duplicated segment. In 2 cases the lesion was in the ascending colon[11,24] and in 1 case in the cecum.[6]

SUMMARY

A case is reported of cystic duplication

of the hindgut observed in a 57 year old female in whom vague abdominal discomfort in the right side of the abdomen was the only symptom. The lesion roentgenologically appeared as a retroperitoneal tumor. The colonic duplication was removed surgically and the diagnosis confirmed histologically.

The theories on the pathogenesis of enteric duplications, and the literature on this entity are reviewed.

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PERIBILIARY FAT*

A NEW ROENTGENOGRAPHIC FINDING

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IN 1972 intravenous cholangiography was performed on a patient suspected clinically of having pancreatitis and a common duct stone (Case 11). On the preliminary roentgenogram and on the intravenous cholangiogram, a curved lucency was noted in the right upper quadrant which was initially felt to represent gas within the biliary system. Subsequently, during the course of the study, a normal biliary system was visualized and the lucency was seen to occur at a bifurcation in the right hepatic duct; it was postulated that this might represent fat adjacent to the biliary structures simulating gas within the biliary tree. Since that time we have accumulated 11 additional cases which demonstrate the same phenomenon.

There have been numerous previous reports related to the role of intra-abdominal fat in the roentgenographic visualization of normal organs and in the diagnosis of intra-abdominal pathologic conditions. However, a review of the literature showed no previous description of the roentgenographic appearance of peribiliary fat.

The purpose of this paper is to call attention to the fact that right upper quadrant

FIG. 1. The liver has been elevated demonstrating the gallbladder (open arrows) and abundant fat around the common bile duct (closed arrows).

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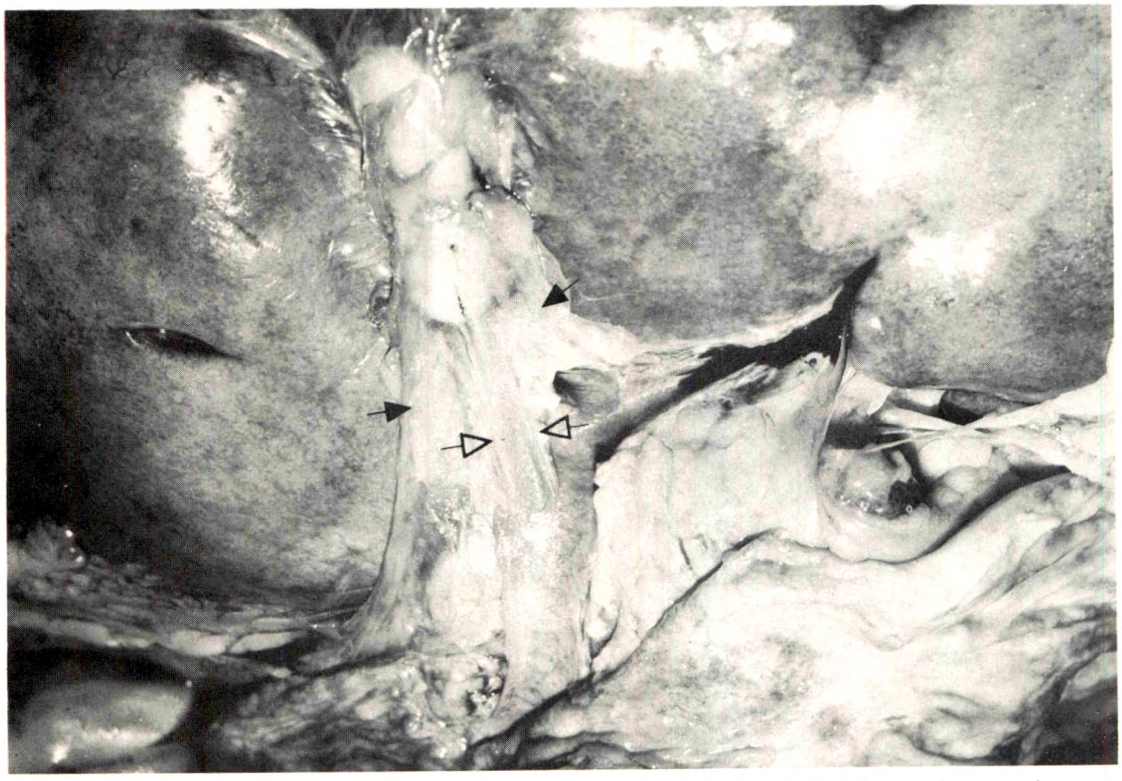

Fig. 2. The common bile duct has been opened (open arrows) and abundant fat can be seen about the duct (closed arrows).

lucencies in the area of the liver, adjacent to the bile ducts, may be seen and should be recognized as peribiliary fat and not confused with gas in the biliary tree or portal systems.

The plain film roentgenographic visualization of intra-abdominal structures is made possible by the silhouetting effect of adjacent fat or intraluminal gas. The psoas muscles are seen because of the presence of adjacent fat and the kidneys are visible because of their enveloping perirenal fat.[6] Whalen *et al.*[7] discussed what was termed the "extraperitoneal perivisceral fat pad" and its role in the roentgenologic visualization of abdominal organs.

The extraperitoneal fat lines have been utilized frequently in the roentgen diagnosis of free intraperitoneal fluid. The diagnosis of free fluid within the pelvis may be suspected when there is visualization of the perivesical fat over the dome of the bladder.[1] Evaluation of the flank stripe, which uses the extraperitoneal or properitoneal fat, has been shown to be of great usefulness.[1–3,5] Visualization of the inferolateral

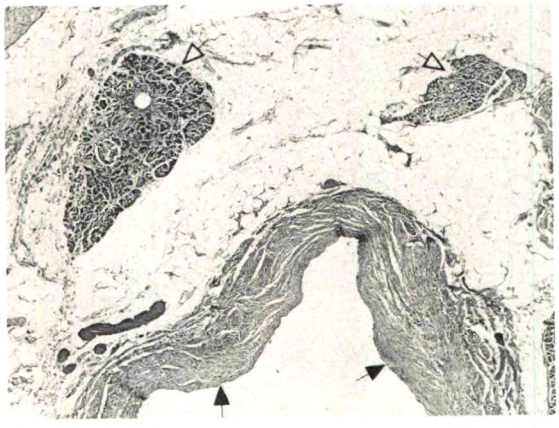

Fig. 3. Microscopic study showing a portion of the common bile duct (closed arrows) near the pancreas. Pancreatic tissue can be seen on this section (open arrows) and the adjacent fat is readily apparent.

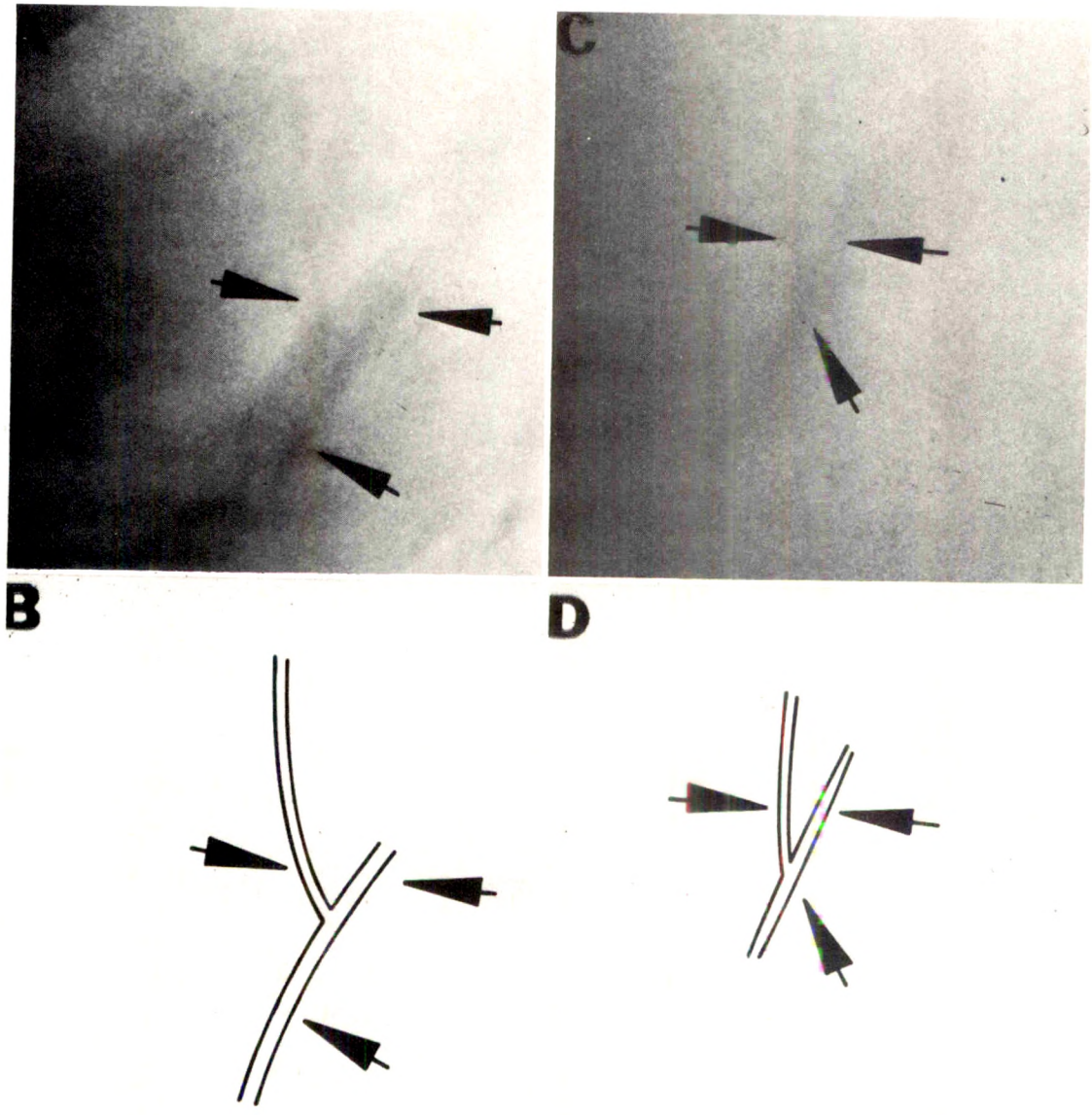

FIG. 4. Case 1. (*A*) Preliminary roentgenogram of the right upper quadrant, demonstrating branching right upper quadrant lucencies. (*B*) Line drawing of the branching right upper quadrant lucencies seen on the preliminary roentgenogram. (*C*) Tomographic section of the right upper quadrant demonstrating the branching lucency, due to peribiliary fat. (*D*) Line drawing of the branching lucency seen on the tomographic section of the right upper quadrant.

edge of the liver (the hepatic angle) has also been described as a useful sign in the roentgenographic diagnosis of intraperitoneal fluid. Margulies and Stoane[4] feel that the visualization of this portion of the liver is due to its close proximity to the greater omentum and pericolic fat. Whalen *et al.*,[7] however, believe that the angle represents the most posterior portion of the inferior edge of the liver which is visible because of its close relationship to the surrounding posterior perivisceral fat. We support the latter concept and believe that the extension of this posterior extraperitoneal fat

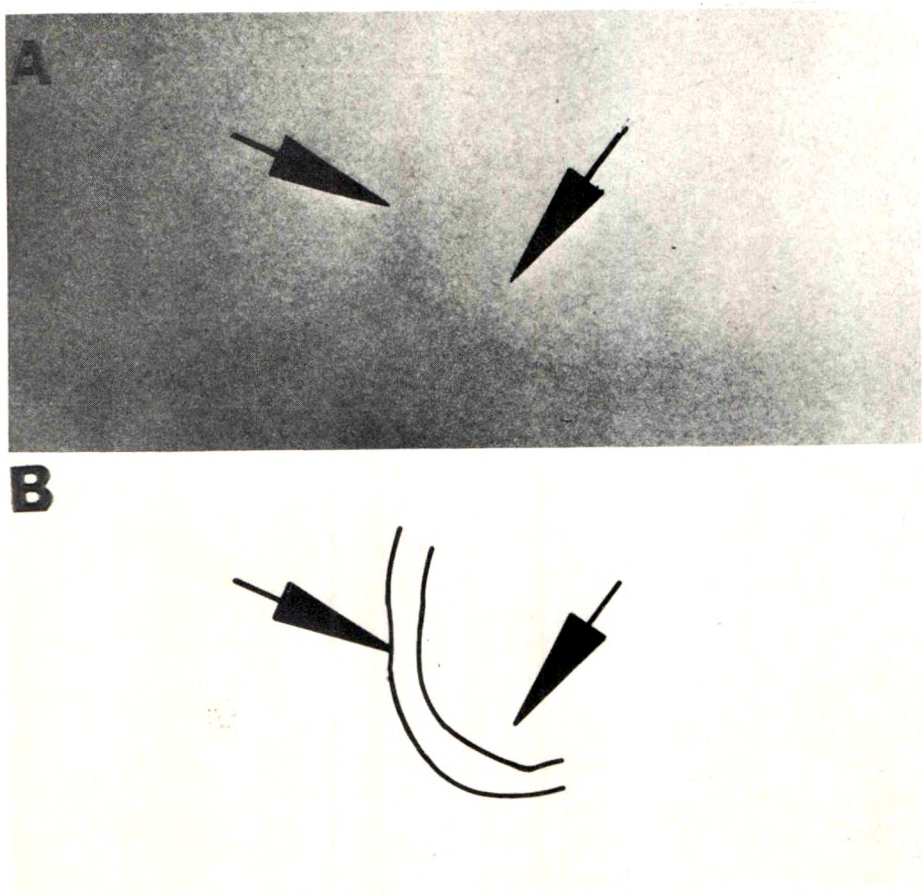

Fig. 5. Case 11. (*A*) Tomographic section obtained on February 13, 1974, showing a curved lucency on an oral cholecystogram where there was nonvisualization of the gallbladder and common bile duct. (*B*) Line drawing of the curved lucency seen on the tomographic section.

along the biliary ducts, up to their entrance into the liver, is responsible for the roentgenographic findings described in this paper.

Fat adjacent to the bile ducts presents roentgenographically either as branching or linear lucencies on plain films of the right upper quadrant or as lucencies adjacent to the bile ducts on intravenous cholangiograms or oral cholecystograms. This lucency is best seen adjacent to the common hepatic and the common bile duct. When the ducts are opacified, the increased density provides more contrast, permitting even better visualization of the peribiliary fat.

In some of our early cases, the fat caused lucencies which simulated gas to such a degree that it was considered as a primary diagnosis. However, the patients had no discernible reason to have gas within the biliary tree as they had had no previous causative type biliary or pancreatic surgery, and, subsequently, possible etiologic biliary and pancreatic diseases were excluded clinically. In addition, upper gastrointestinal studies showed a normal descending duodenum with no reflux of barium into the common bile duct. It was also noted that the linear lucencies did not appear to have quite the degree of radiolucency which would be expected with gas.

The biliary system was examined at numerous autopsies, and after multiple dissections it became apparent that fat nor-

FIG. 6. Case II. Tomographic section obtained during intravenous cholangiography on February 14, 1973, showing the junction of the common and left hepatic duct where the curved lucency had previously been seen (arrows) in Figure 5. The peribiliary fat adjacent to the common bile ducts is well demonstrated on this tomographic section.

mally occurs around the bile ducts up to their entrance into the liver (Fig. 1; 2; and 3). This was seen as an extension of the extraperitoneal fat, and the quantity of fat was roughly proportional to the amount of fat present in the remainder of the subject's body. Thus, the findings of right upper quadrant lucencies due to peribiliary fat are seen roentgenographically most frequently in obese individuals.

In some cases a single linear lucency or a branching lucency was observed. On the subsequent intravenous cholangiograms this was seen to be due to fat adjacent to one side of the bile duct or adjacent to a bile duct bifurcation (Fig. 4, *A–D*; 6; and 9, *A* and *B*). In other cases, parallel linear lucencies were seen with subsequent opacification of the common bile duct between these lucencies during the course of an intravenous cholangiogram. In these cases, the width of the common bile duct could be measured on the preliminary films of the intravenous cholangiogram (Fig. 7, *A* and *B*; and 8, *A* and *B*). In several cases the amount of fat adjacent to the visualized common bile duct was substantial (Fig. 6;

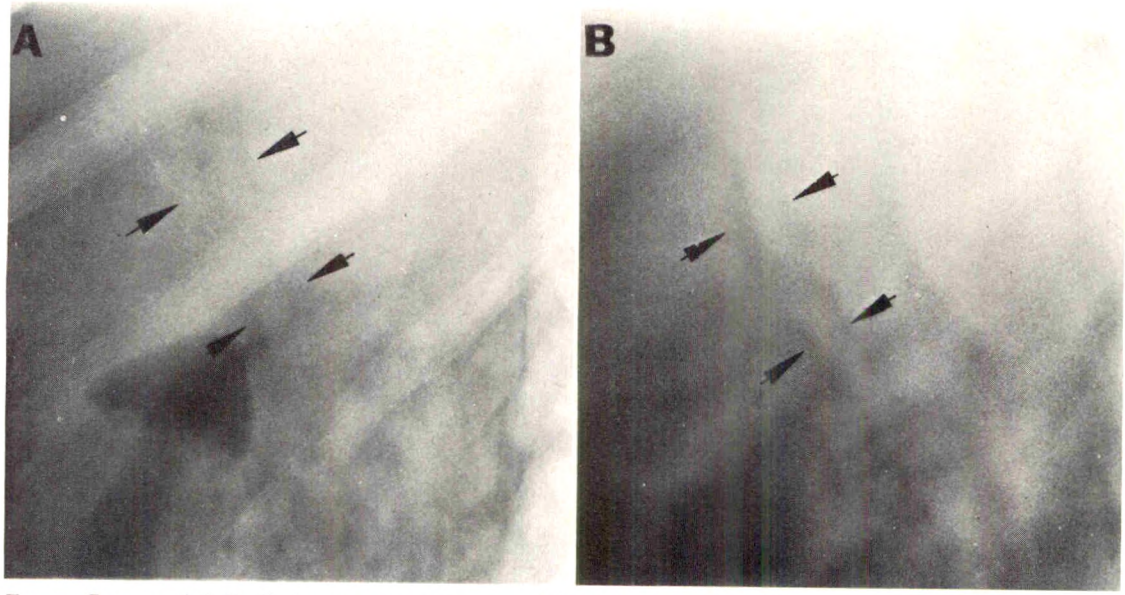

FIG. 7. Case III. (*A*) Preliminary roentgenogram of the right upper quadrant, where the common bile duct diameter can be measured. (*B*) Tomographic section obtained during intravenous cholangiography with visualization of the common bile duct between the previously described linear lucencies. The peribiliary fat adjacent to the common bile and common hepatic ducts is well demonstrated on this tomographic section.

and 7, *A* and *B*). These lucencies should not be confused with portal venous gas because of the latter's more peripheral location.

A recent case, however, made it apparent that one must be cautious about attributing all parallel linear right upper quadrant lucencies to fat adjacent to the extrahepatic bile ducts. We recently performed intravenous cholangiography and a band-like density with faint bordering lucencies was seen in the approximate position of the common bile duct. This was seen on the preliminary roentgenogram as well as on the films exposed during the course of intravenous cholangiography, during which no opacification of the bile ducts occurred. On close inspection, it was noted that these shadows extended more superiorly than would the extrahepatic bile ducts. It was postulated that this shadow might be due to a noncalcified left costal cartilage which was projected over the liver because of the right posterior oblique position used for the intravenous cholangiogram. To clarify this, lead markers were placed over the left lower costal cartilage and a repeat right posterior oblique roentgenogram was obtained. This roentgenogram demonstrated that in fact the linear shadow was due to the projection of the noncalcified left lower costal cartilage (Fig. 10, *A* and *B*). The density could not be identified in the tomograms at the expected level of the bile ducts. Tomograms taken at the level of the lower rib cartilages clearly showed that these structures were responsible for the density noted. Since the bile ducts visualized by peribiliary fat are extrahepatic, their visualization is at a lower level in relation to the liver than the shadow cast by costal cartilage. Of course, when the costal cartilages are calcified there is no problem in identification.

The course and location of the common bile duct are somewhat variable. At times, there can be confusing linear densities in the right upper quadrant. This is especially noticeable when tomographic sections of the right upper quadrant are obtained to visualize a faintly opacified bile duct. Therefore, another use of the peribiliary fat line is in localization of the common bile duct,

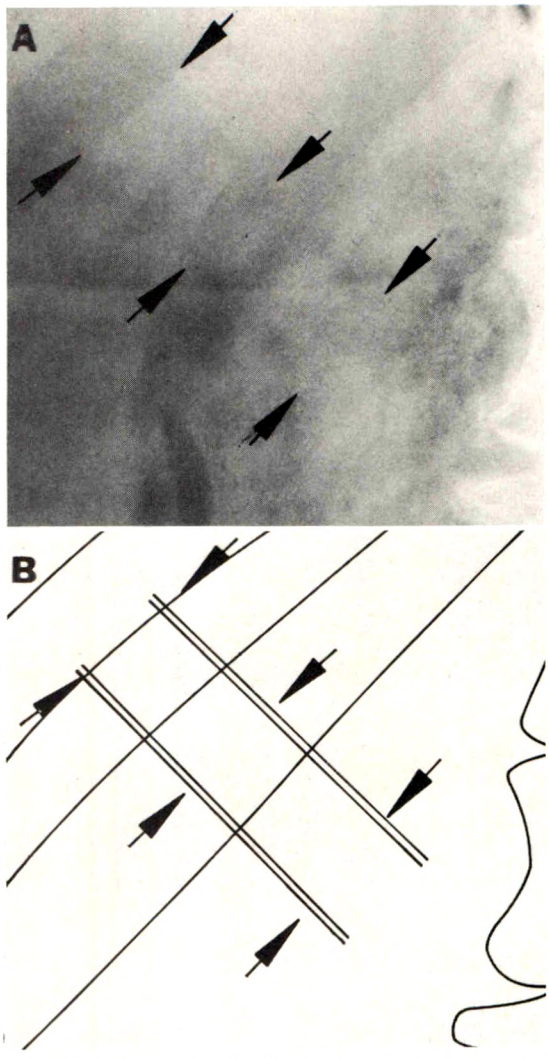

Fig. 8. Case iv. (*A*) Preliminary roentgenogram of the right upper quadrant, where the common bile duct diameter can be measured. A tomographic section obtained after a double dose oral cholecystogram showed the common bile duct faintly visualized between the linear lucencies. (*B*) Line drawing showing the parallel linear lucencies due to the peribiliary fat.

when it is only faintly visualized during intravenous cholangiography or oral cholecystography.

We have had 2 cases where the common bile duct was difficult to discern, but after noting the linear lucency it could be much more readily and accurately appreciated.

Two typical case histories are described below:

Case 1. V.A. A 54 year old Mexican Ameri-

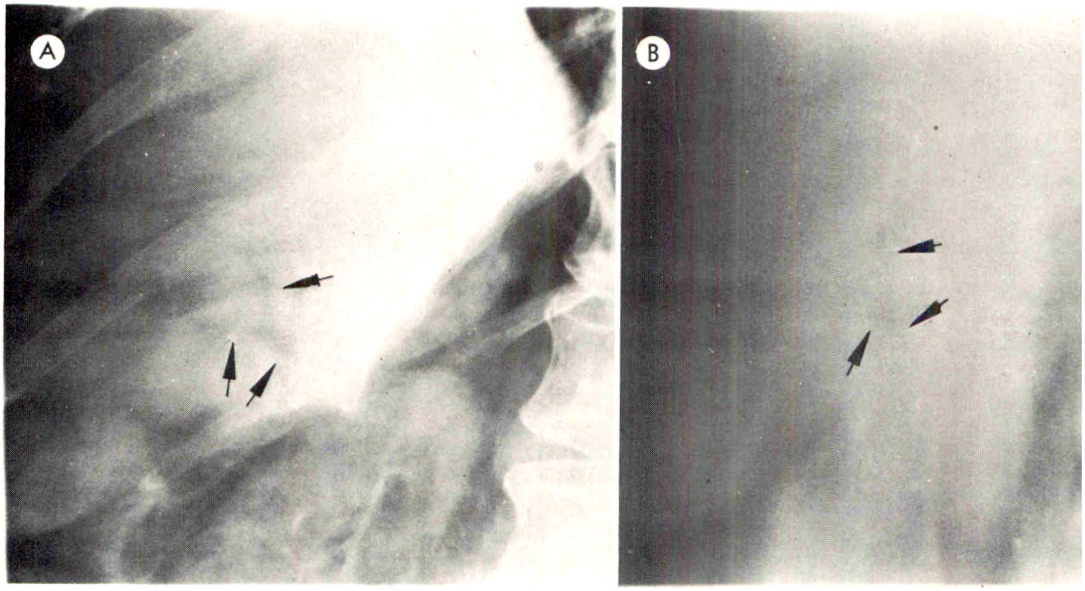

FIG. 9. Case v. (*A*) Preliminary roentgenogram of the right upper quadrant showing branching lucenc (*B*) Tomographic section obtained before an intravenous cholangiogram showing the branching luce to better advantage. Subsequently, the junction of the right and left hepatic ducts was seen adjacen these branching lucencies.

can female was admitted on January 12, 1973 with a history of diabetes mellitus, a right thigh abscess, and osteomyelitis at L4, L5. The patient's past history included a cholecystectomy in 1965 for gallbladder calculi. The patient had no biliary tract symptoms, and the contrast studies of the biliary system were requested to confirm the absence of the gallbladder. February 13, 1973 the patient had an c cholecystogram with nonvisualization of gallbladder. At this time branching lucenc were noted in the right upper quadrant (I 4, *A–D*). On February 14, 1973 an int venous cholangiogram showed good visuali

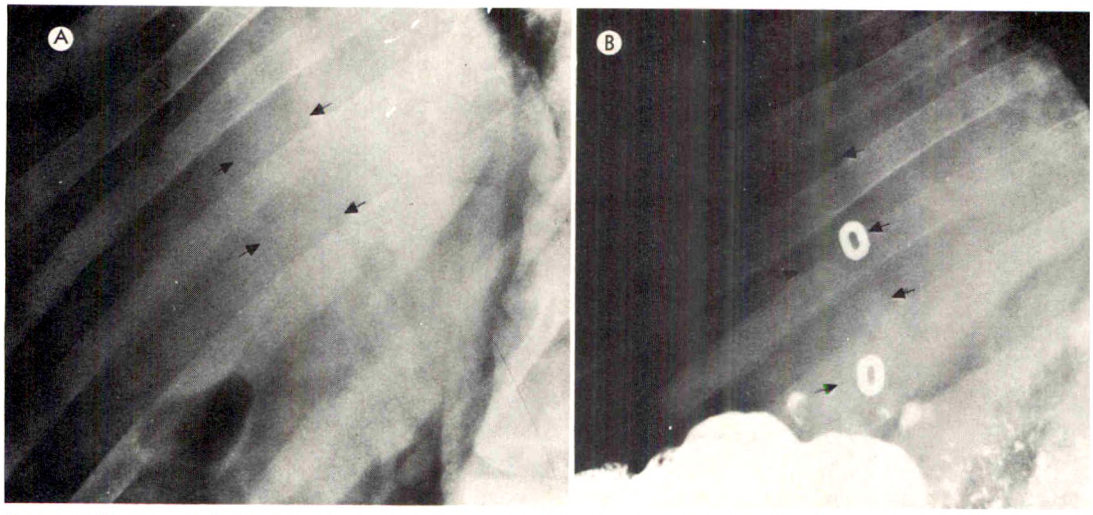

FIG. 10. Case VI. (*A*) An 80 minute intravenous cholangiogram showing the linear shadow (closed arro projected in the approximate location of the common bile duct. The xiphoid process is identified by the o arrow. (*B*) Repeat right post oblique projection with lead markers on the left lower costal cartilage. T barium in the lower portion of the roentgenogram is from a previous upper gastrointestinal series.

tion of a normal common bile duct with abundant adjacent fat. Also, there was seen to be a branching of the right hepatic duct where the previously noted branching lucency had been seen.

Case II. H.A. A 62 year old Caucasian male entered the hospital with a clinical diagnosis of pancreatitis and possible common duct stones. Intravenous cholangiography was performed and a curved lucency in the right upper quadrant was seen on the preliminary film (Fig. 5, *A* and *B*). The intravenous cholangiogram showed that this lucency represented fat located at the junction of the common hepatic and left hepatic ducts. There also was noted to be a moderate amount of fat adjacent to the common hepatic and common bile ducts after opacification of these ducts. The gallbladder was seen to contain multiple calculi and the patient had a subsequent cholecystectomy.

SUMMARY

Eleven cases of branching or linear right upper quadrant lucencies due to peribiliary fat have recently been seen at LAC/USC Medical Center. No previous report of this entity was found in a review of the literature.

The significance of these lucencies is that branching or linear right upper quadrant lucencies are not necessarily gas within the biliary or portal system, but may be due to prominent peribiliary fat. These lucencies may also be of help in identifying, locating and measuring the diameter of the common bile duct when it is only faintly visualized on an intravenous cholangiogram or when its anatomic course is atypical.

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ANGIOGRAPHIC EVALUATION OF PATIENTS WITH CHRONIC GASTROINTESTINAL BLEEDING*

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MOST radiologists are familiar with the difficulties associated with evaluation of patients with chronic gastrointestinal bleeding. Much time and attention have been given to this problem, both clinically and in the radiologic literature.[3,8,9,12,13] The traditional approach with barium examination is still valid and usually is the cheapest, easiest, and most productive means of study; used in association with various endoscopic examinations, the diagnostic yield is quite high. Even so, these methods still frequently fail to detect the causative lesion. In the past few years, however, angiographic techniques have expanded the scope of roentgenologic investigation and have increased the diagnostic yield still further in these problem cases. Many reports have emphasized the usefulness of angiography in detecting obscure lesions,[5,8–11,14] yet it is still difficult to get a clear picture of the absolute success rate of angiography in identifying a source of chronic gastrointestinal bleeding. In making this report the authors set out to answer one basic question: What are the chances that an obscure site of gastrointestinal bleeding can be found by angiography in a group of patients who have been evaluated reasonably thoroughly and in whom the source of bleeding has not yet been found?

Our approach to the problem in general has been to reserve angiography for patients with chronic recurrent gastrointestinal bleeding only after more traditional methods have failed to detect the source of bleeding. In such patients we expect to find some type of structural lesion in the bowel rather than extravasation of contrast material into the bowel lumen.

MATERIAL AND METHOD

Details of Patients. Review of the records and roentgenograms of all patients who had angiography for chronic and recurrent gastrointestinal bleeding at the Mayo Clinic from 1969 through the first 6 months of 1974 yielded a study group of 88 patients. Their ages ranged from 4 to 79 years (Table I). The sex distribution was approximately equal; there were 45 males and 43 females. The duration of symptoms ranged from 3 months to 22 years; it was 5 years or longer in 28 patients (Table II). Many of the patients had had one or more previous surgical procedures (Table III). These pro-

TABLE I

AGE DISTRIBUTION

Decade	No. of Patients
0–9	4
10–19	5
20–29	8
30–39	5
40–49	12
50–59	21
60–69	19
70–79	14

TABLE II

DURATION OF SYMPTOMS

Duration (yr.)	No. of Patients
0–0.5	15
0.5–1	15
1–2	17
2–3	11
3–4	2
≥5	28

* Presented at the Seventy-fifth Annual Meeting of the American Roentgen Ray Society, San Francisco, California, September 24–27, 1974.
From the Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

Table III

FREQUENCY OF PRIOR SURGERY

No. of Procedures	No. of Patients
One	29
Two or more	15
None	44

cedures, which were not curative, included laparotomy with negative findings, vagotomy and pyloroplasty, gastric resection, or partial colectomy.

At the time of angiography, the patients did not have a diagnosis of a lesion that seemed to be responsible for the bleeding and none of them were bleeding actively. In 74 of the 88 patients, clinical evaluation for a source of blood loss before angiography had been entirely negative (Table IV). The clinical investigation usually included an examination of the upper gastrointestinal tract, the small intestine, and the colon, together with various endoscopic and proctologic examinations. In 13 of the remaining 14 cases, a diagnosis had been made but it seemed doubtful that the patient was bleeding from the lesion; at angiography in these 13, either no lesion or a different structural lesion was eventually found. In the case of the remaining 1 patient, a complete investigation had not been done before angiography; the reason was that in the case of the patient's sister, clinical investigation for chronic gastrointestinal bleeding had been negative and the offending lesion had been found only by angiography.

Table IV

PREANGIOGRAPHIC EVALUATION

Details of Evaluation		No. of Patients
Positive diagnosis		13
Diaphragmatic hernia	2	
Diverticulosis	2	
Duodenal ulcer	1	
Gastric ulcer	1	
Colon polyp	2	
Alkaline gastritis	1	
Carcinoma of pancreas	1	
Meckel's diverticulum	1	
Esophageal varices	1	
Blood dyscrasia	1	
Negative evaluation		74
No prior evaluation		1
Total		88

Table V

LESIONS ASSOCIATED WITH 41 POSITIVE ANGIOGRAMS

Lesion		No. of Patients
Arteriovenous malformations		21
Duodenum	4 (2*)	
Jejunum	5 (2*)	
Cecum	9 (1*)	
Ascending colon	2	
Omentum	1	
Tumors of bowel		5
Leiomyoma	2	
Stomach	1	
Ileum	1	
Carcinoma of colon	2	
Reticulum cell sarcoma of jejunum	1	
Visceral artery aneurysms		4
Gastroduodenal artery	1	
Superior mesenteric artery branches	3	
Polyps		3
Ileum	2	
Colon	1	
Meckel's diverticulum		2
Gastritis		2
Regional enteritis		1
Nonspecific ulcer of ileum		1
Cavernous hemangioma of rectosigmoid		1
Islet-cell tumor of pancreas		1

* Not surgically proven.

Excluded from this series were any patients with a preangiographic diagnosis that seemed to be consistent with a source of the bleeding. Patients with esophageal and gastric varices and known tumors of the bowel were thus not included in the study.

Technique of Angiography. All studies were done by retrograde femoral selective catheter techniques using stereoscopic serial filming and magnification and subtraction when appropriate.

RESULTS

In this group of 88 angiographic studies, 41 positive and 47 negative diagnoses were made (Tables V and VI). There were no

TABLE VI

OUTCOME OF 47 PATIENTS WITH NEGATIVE ANGIOGRAMS

Outcome	No. of Patients		
Presumed true negative			41
No surgical procedure		27	
Surgical procedure performed		14	
Exploration negative	12		
Exploration positive	2		
Duodenal ulcer	1		
Diverticulosis	1		
False-negative			6*

* Subsequent investigation revealed the following abnormalities in this group: carcinoma (2), leiomyoma (1), Meckel's diverticulum (1), Crohn's disease of transverse colon (1), and phlebectasia (1).

false-positive results and there were 6 false-negative results (Table VI).

The 41 positive diagnoses covered a multiplicity of lesions (Table V). Of these 41 lesions, 36 were verified surgically and 5 were not so confirmed.

Evaluation of the cases with a negative diagnosis was difficult because in 27 cases a confirmatory surgical procedure was not performed (Table VI). Among the 14 other patients in this group with a negative angiographic diagnosis who had surgery, 12 were found to have no abnormality at laparotomy, 1 was found to have a duodenal ulcer deformity as the only abnormality, and 1 was found to have colonic diverticulosis as the only finding (Table VI). In neither of the 2 latter cases did the abnormality seem to be the source of bleeding.

With respect to the 6 definite false-negative diagnoses, subsequent investigation revealed the lesions that had caused the bleeding. These lesions were the following: carcinoma (2), leiomyoma (1), Meckel's diverticulum (1), Crohn's disease of the transverse colon (1), and phlebectasia (1). Review of the angiograms showed that, although the examinations were of reasonably good quality, there were no angiographic

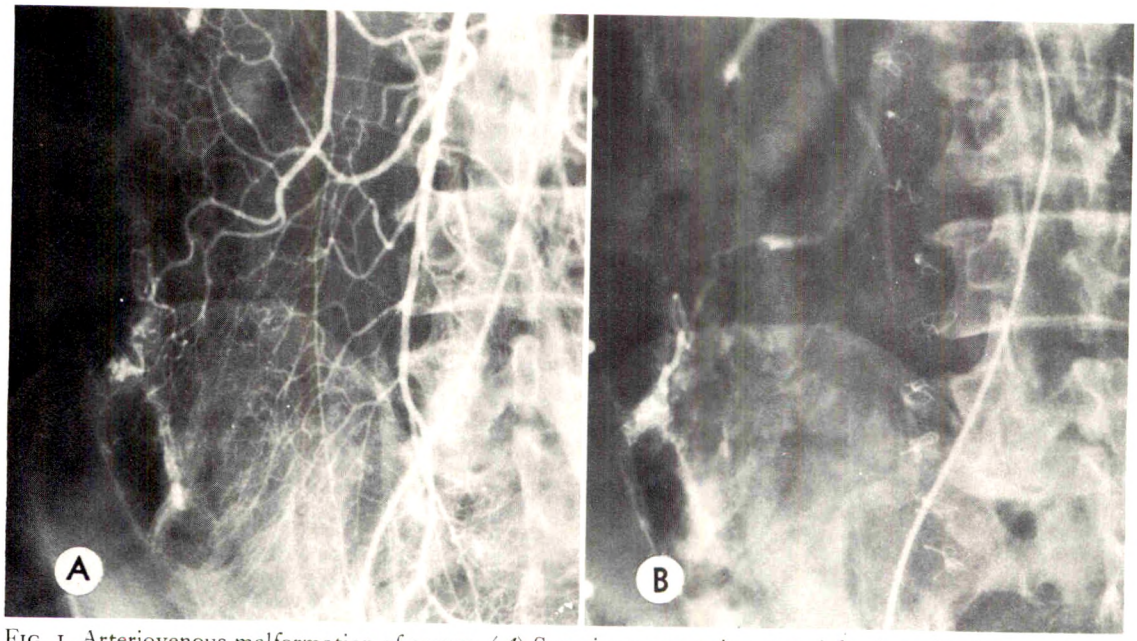

FIG. 1. Arteriovenous malformation of cecum. (*A*) Superior mesenteric artery injection, showing small network of abnormal vascularity in cecum and ascending colon. (*B*) Venous phase, showing prominent draining vein.

The patient was a 61 year old man with a 2 year history of chronic recurrent gastrointestinal bleeding. Results of barium studies and proctoscopic examination were negative, as was laparotomy 1 year prior to angiography.

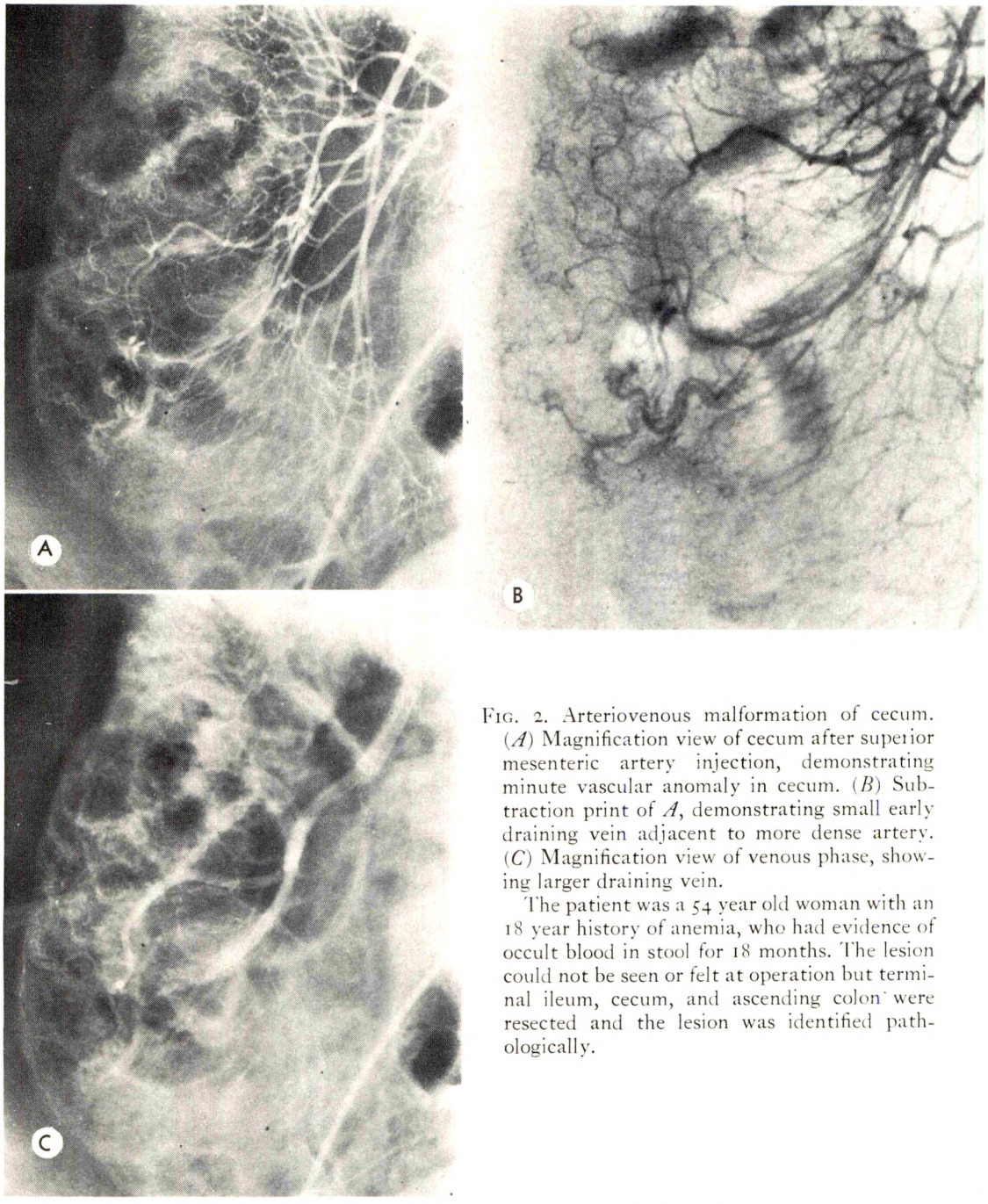

Fig. 2. Arteriovenous malformation of cecum. (*A*) Magnification view of cecum after superior mesenteric artery injection, demonstrating minute vascular anomaly in cecum. (*B*) Subtraction print of *A*, demonstrating small early draining vein adjacent to more dense artery. (*C*) Magnification view of venous phase, showing larger draining vein.

The patient was a 54 year old woman with an 18 year history of anemia, who had evidence of occult blood in stool for 18 months. The lesion could not be seen or felt at operation but terminal ileum, cecum, and ascending colon were resected and the lesion was identified pathologically.

abnormalities present—even when examined in retrospect.

DISCUSSION

The results of the study were particularly encouraging and gratifying, for it was not anticipated that the yield of positive diagnoses would be quite so high. There is, however, an element of uncertainty in the evaluation of the positive cases because it is difficult to be sure that the angiographically identified lesions were, in fact, responsible

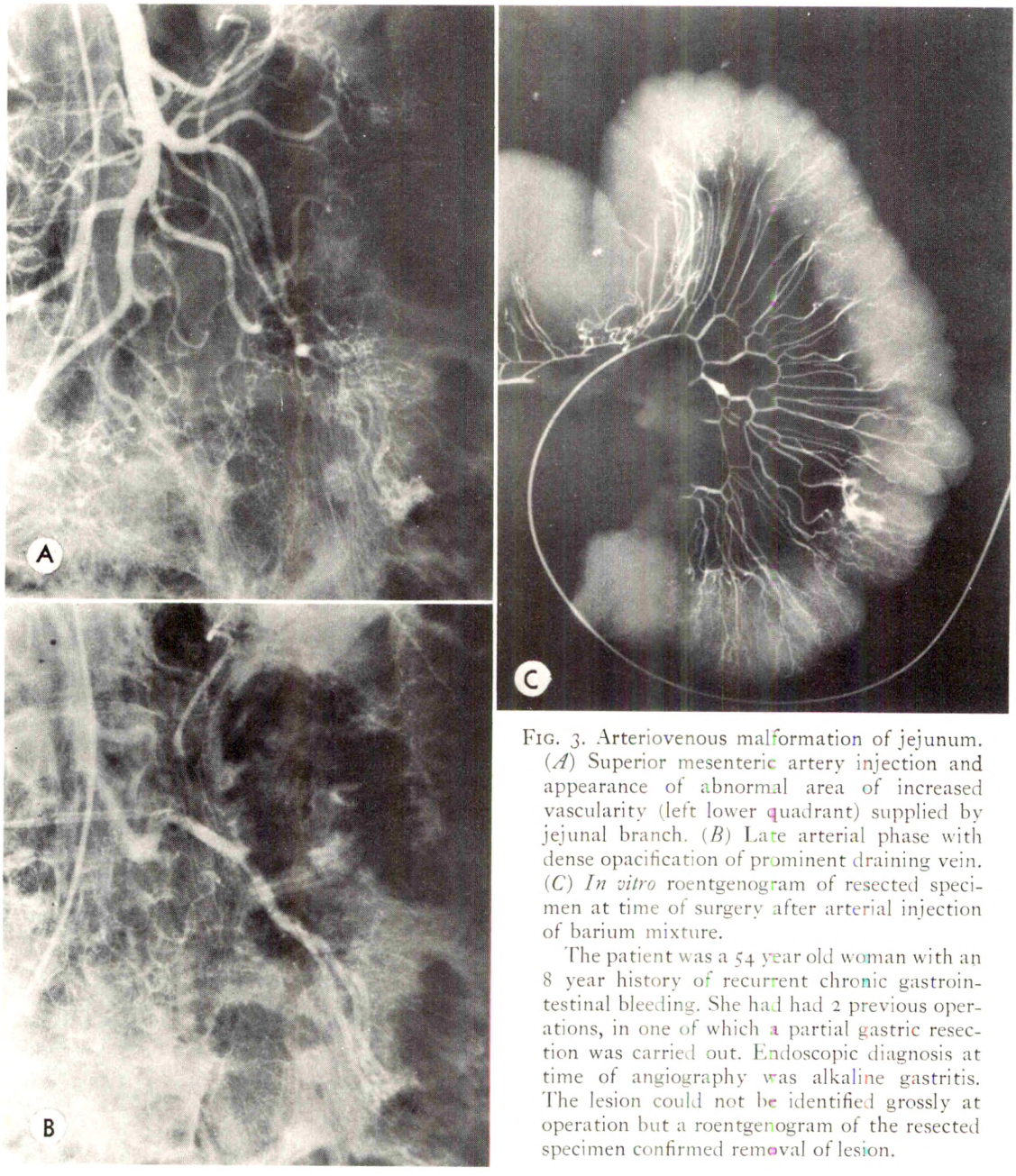

FIG. 3. Arteriovenous malformation of jejunum. (*A*) Superior mesenteric artery injection and appearance of abnormal area of increased vascularity (left lower quadrant) supplied by jejunal branch. (*B*) Late arterial phase with dense opacification of prominent draining vein. (*C*) *In vitro* roentgenogram of resected specimen at time of surgery after arterial injection of barium mixture.

The patient was a 54 year old woman with an 8 year history of recurrent chronic gastrointestinal bleeding. She had had 2 previous operations, in one of which a partial gastric resection was carried out. Endoscopic diagnosis at time of angiography was alkaline gastritis. The lesion could not be identified grossly at operation but a roentgenogram of the resected specimen confirmed removal of lesion.

for the bleeding. Moreover, although clinical follow-up was not complete for every patient, among those in whom resection was performed and who have returned for follow-up, a cure has been effected in all but one. The exception was a patient who continued to bleed after resection of a cecal arteriovenous malformation until he was found to have a duodenal ulcer 2 years later.

It is worth considering the discovered lesions in more detail.

Arteriovenous malformations have been particularly well documented in the literature[1,7] and, as expected, approximately one-half (21 of 41) of our positive diagnoses

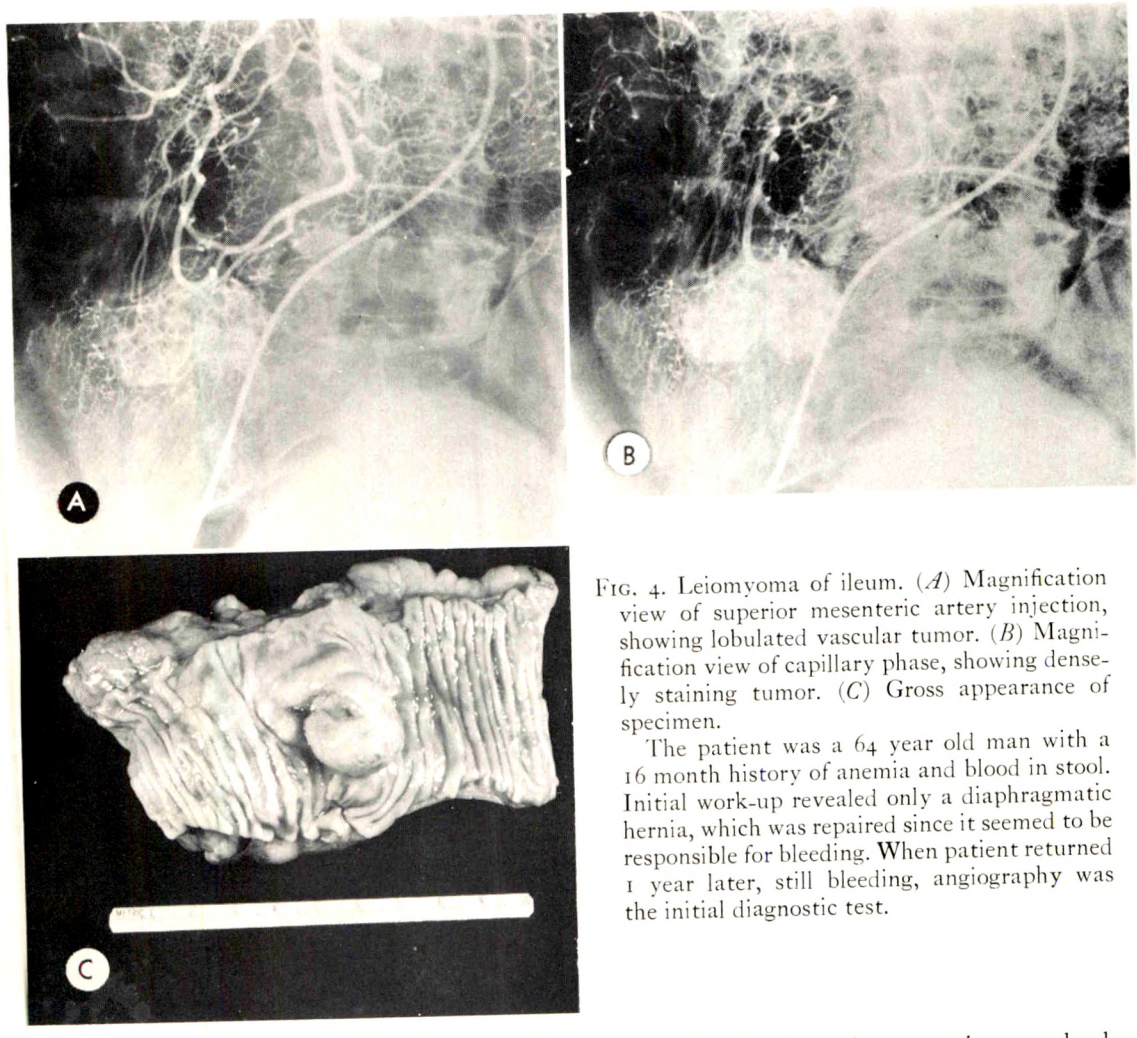

Fig. 4. Leiomyoma of ileum. (*A*) Magnification view of superior mesenteric artery injection, showing lobulated vascular tumor. (*B*) Magnification view of capillary phase, showing densely staining tumor. (*C*) Gross appearance of specimen.

The patient was a 64 year old man with a 16 month history of anemia and blood in stool. Initial work-up revealed only a diaphragmatic hernia, which was repaired since it seemed to be responsible for bleeding. When patient returned 1 year later, still bleeding, angiography was the initial diagnostic test.

were of arteriovenous malformations. The histories of the patients with arteriovenous malformations ranged in duration from 4 months to 22 years. Nine patients had had no prior surgical procedures, but the remaining 12 patients had undergone a total of 18 negative explorations. It is unfortunate that 5 of the arteriovenous malformations have not been verified surgically, but the angiographic findings are still reasonably conclusive. In 1 patient, who was seen rather early in the series, the lesion was not identified at operation and the angiographically abnormal segment of bowel was not resected. In 2 patients, the malformations were in the retroperitoneal duodenum and it was thought that radical surgery was not indicated. In the other 2 patients, who had malformations of the jejunum and of the cecum, respectively, it was elected to wait until the symptoms were more troublesome before proceeding with surgery. Two of these 5 patients have had continued blood loss; no follow-up information is available for the other 3 patients.

The distribution of the arteriovenous malformations within the bowel is in accord with that of other series, the majority being found in the cecum and the right colon (Fig. 1, *A* and *B*; and 2, *A–C*). The omental arteriovenous malformation was unusual in that it was not congenital but probably secondary to a traumatic liver biopsy.[2,15] The lesion was contained entirely

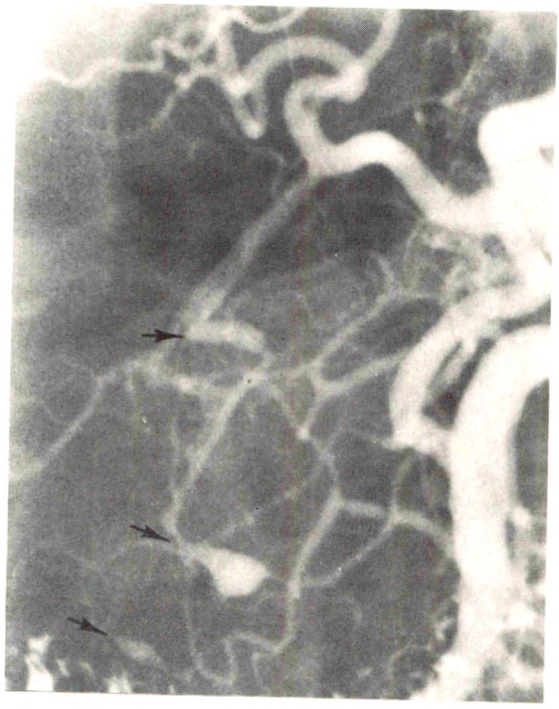

FIG. 5. Three separate fusiform aneurysms of gastroduodenal artery (*arrows*) in angiogram of pancreatic arcade branches and gastroduodenal artery.

The patient was a 70 year old woman receiving anticoagulants, who had guaiac-positive stools and anemia. Preangiographic evaluation showed 2 polyps in the colon. At operation, a large retroperitoneal hematoma apparently originated in the region of the aneurysms.

in the omentum and was resected; bowel resection was not necessary.

We emphasize that angiography is the only reliable method to detect these arteriovenous malformations, for they are difficult to find at operation and, indeed, difficult to find even in the resected specimens. We make use of *in vitro* specimen radiography at the time of operation to be certain that the lesion is contained in the resected specimen (Fig. 3, *A–C*).

The 5 instances of tumor occurred in patients who had undergone reasonably thorough investigation for chronic gastrointestinal bleeding before angiography. However, in 4 of these patients, the most recent negative barium studies had been performed several months before angiography. The 2 leiomyomas were small; the diameter of the one in the stomach measured 1 cm. and that in the ileum, 4 cm. The latter was visualized on the barium examination after angiography had been performed, but the last previous negative small-bowel examination had been 12 months prior to angiography and preceded surgery for repair of a diaphragmatic hernia (Fig. 4, *A–C*). The 2 carcinomas were 2 and 4 cm. in diameter, respectively, and had not been detected on colon examinations before angiography. In fact, the lesion in the cecum was originally discovered angiographically 2 years before surgery. At the time of angiography, the clinician believed that the angiographic findings were not sufficiently conclusive to warrant exploration. When the patient returned 2 years later—still with chronic gastrointestinal bleeding—he had a large extensive neoplasm in the cecum that was obvious by that time on the colon examination. The fifth tumor was a reticulum cell sarcoma in a patient whose original small bowel examination had been interpreted as being suggestive of submucosal hemorrhage.

The 4 cases of visceral artery aneurysms are problematic. The potential of these aneurysms for bleeding has been stressed,[4] and we have seen active bleeding from similar lesions. It is difficult to be sure that the aneurysms that were found in these chronically bleeding patients were actually the source of bleeding, but the fact remains that they were the only positive findings. In addition to the aneurysms, a retroperitoneal hematoma was found in one (Fig. 5) and a mesenteric hematoma in 2 patients at the time of surgery.

The 3 cases of polyps are interesting in that they were discovered in children (ages 7, 13, and 15 years) and were juvenile retention polyps. Such polyps must be uncommon sources of gastrointestinal bleeding, but all 3 of the patients, 2 of whom were sisters, bled no more after operation (Fig. 6, *A* and *B*).

The 2 Meckel's diverticula were angiographically manifest by increased vascularity and staining in the ileum (Fig. 7, *A–C*).

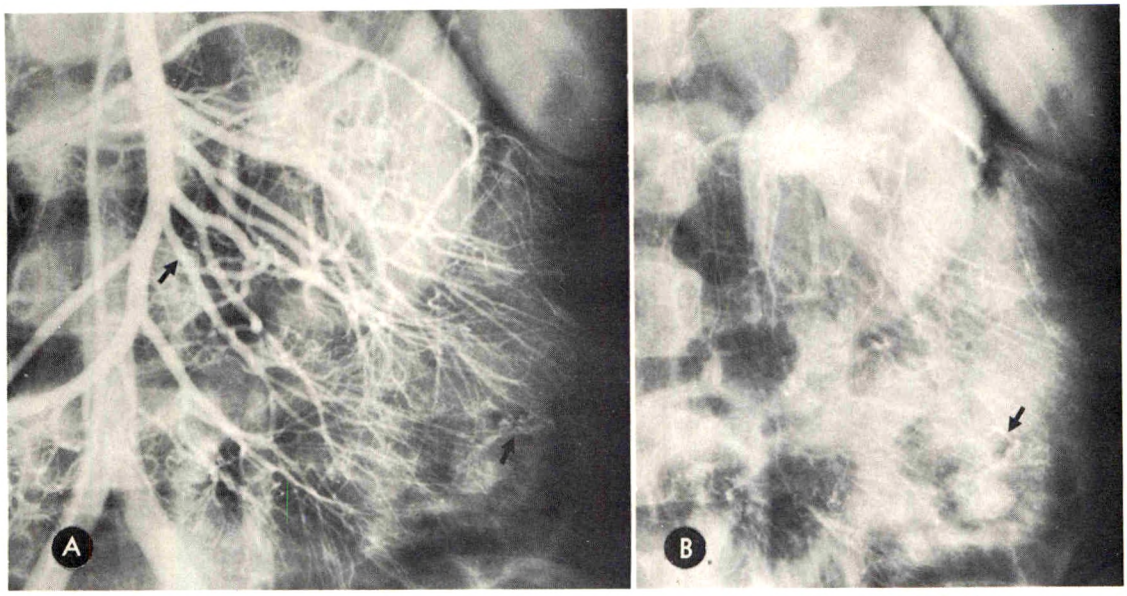

Fig. 6. Juvenile retention polyp in jejunum. (*A*) Superior mesenteric injection, showing minimal arterial abnormality (*lower arrow*) in distal portion of jejunal branch (*upper arrow*). (*B*) Magnification of late venous phase, showing small vein draining faintly stained structural mass in bowel lumen (*arrow*); this was found to be a polyp.

The patient was a 7 year old girl with an 18 month history of anemia, fatigue, and stool positive for occult blood. Results of clinical evaluation were negative. At operation a juvenile retention polyp (diameter, 1 cm.) was removed. There was no further blood loss.

The 2 instances of hyperemic and thickened gastric mucosa thought to be gastritis were substantiated by endoscopy, which had not been done prior to angiography in either case. The remaining cases of regional enteritis, nonspecific ulceration of the ileum, vascular islet-cell tumor of the pancreas, and cavernous hemangioma of the rectosigmoid were isolated and straightforward cases.

Evaluation of the 47 negative studies is difficult and disappointing, for among them are 6 false-negative results. The 3 tumors that were found at subsequent operation were rather large and no angiographic changes were present, even in retrospect. Two were exophytic small bowel lesions (1 carcinoma and 1 leiomyoma) and 1 was a carcinoma of the cecum. The other 3 lesions for which the diagnosis was made after angiography included Meckel's diverticulum (detected by a technetium 99m scan), Crohn's disease of the transverse colon (discovered by colonoscopy), and phlebectasia (discovered at operation).

Among the remaining 41 patients in whom no angiographic lesion was found, 32 were discharged with a diagnosis of chronic gastrointestinal bleeding of unknown etiology. In the remaining 9, a presumptive diagnosis of a source of bleeding was made by exclusion. Three patients had diagnoses of blood dyscrasias, 3 of esophageal hiatus hernias, 1 of duodenal ulcer, 1 of colon polyp, and 1 of diverticulosis. Interestingly, in 6 of the 32 patients with a negative diagnosis, there was angiographic evidence of visceral artery stenosis or occlusion with extensive collateral circulation. The possibility of an association of gastrointestinal bleeding with visceral artery occlusive disease has been noted,[6] but this certainly seems difficult to substantiate in view of the many persons with visceral artery stenosis or occlusion who do not have gastrointestinal bleeding.

CONCLUSIONS

This review of our experience with angiography for chronic gastrointestinal bleed-

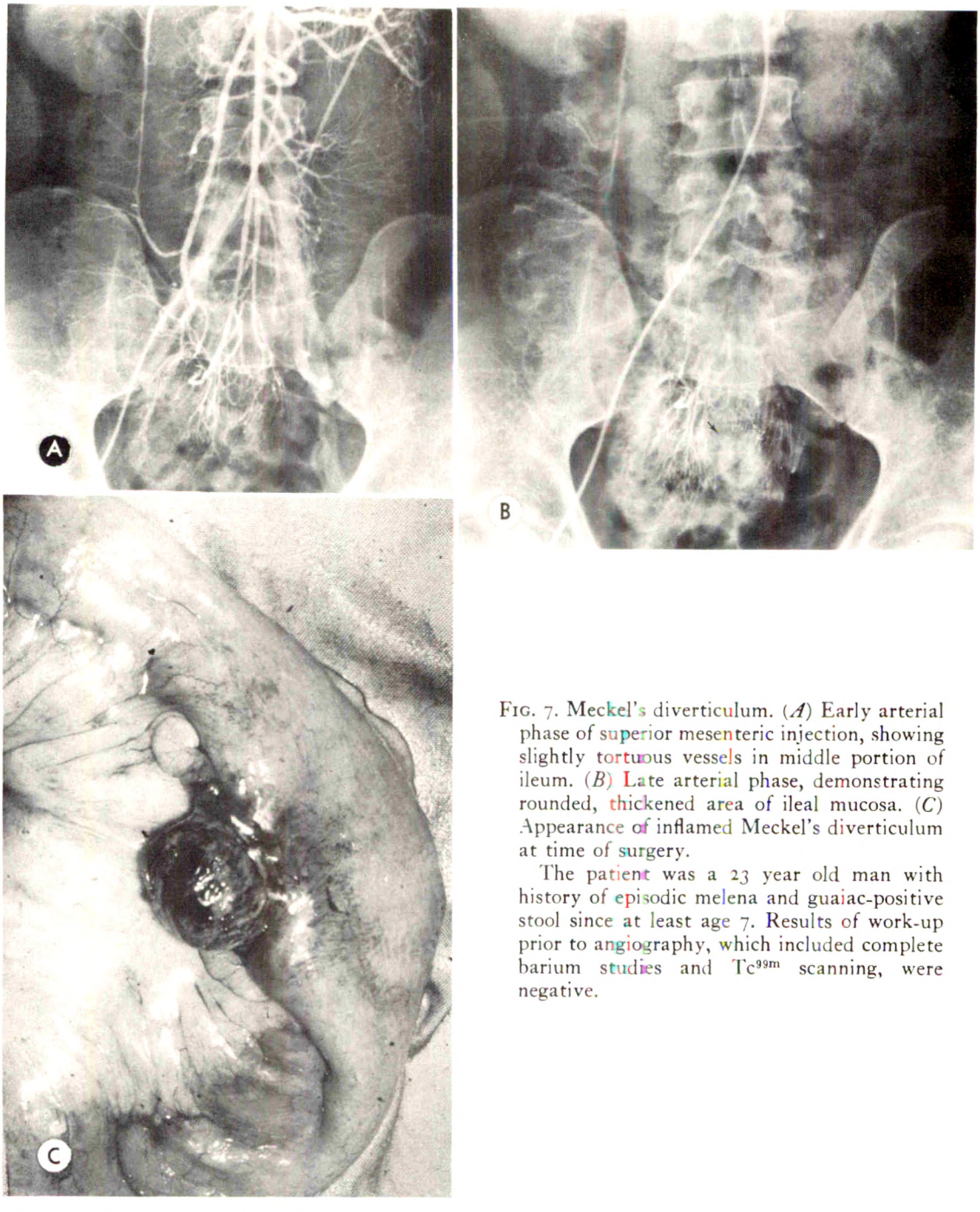

FIG. 7. Meckel's diverticulum. (*A*) Early arterial phase of superior mesenteric injection, showing slightly tortuous vessels in middle portion of ileum. (*B*) Late arterial phase, demonstrating rounded, thickened area of ileal mucosa. (*C*) Appearance of inflamed Meckel's diverticulum at time of surgery.

The patient was a 23 year old man with history of episodic melena and guaiac-positive stool since at least age 7. Results of work-up prior to angiography, which included complete barium studies and Tc^{99m} scanning, were negative.

ing permits us to draw the following conclusions:

1. In patients who have definite chronic bleeding and in whom a thorough clinical investigation has been negative, there is approximately a 45 per cent chance of finding an angiographically identifiable lesion that may be a site of bleeding.

2. In one-half of patients with a positive diagnosis, the lesion is an arteriovenous malformation of the bowel.

3. One-half of the arteriovenous mal-

formations are located in the cecum or ascending colon.

4. The incidence of false-negative examinations (in this series, 6 of 47) is distressingly high.

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A RADIOLOGIC STUDY OF TUBERCULOSIS OF THE ABDOMEN (GASTROINTESTINAL TRACT)

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TUBERCULOSIS of the abdomen is a common medical condition and a major health problem in this country. Reports of the clinical features of the disease as seen in Ibadan have already been documented.[9,11] However, there has been no report of the radiologic featues of this disease from Ibadan.

The purpose of this paper, therefore, is to report the radiologic findings as seen at the University College Hospital, Ibadan, and to assess their value in the diagnosis of the disease.

MATERIAL AND METHOD

The 169 patients selected for this review were only those patients who had been roentgenographed during the process of general investigations and who had been ultimately diagnosed as cases of abdominal tuberculosis. The specific criteria for diagnosis were based on either a positive histologic specimen of the abdominal gland or peritoneum taken at surgery or autopsy, or a positive bacteriologic examination from the stool or the ascitic fluid.

The roentgenograms included a plain film roentgenogram of the abdomen and the chest, and special examinations of the gastrointestinal tract such as barium meal and barium enema studies. All the films were then critically reviewed to assess the different radiologic features of abdominal tuberculosis.

RESULTS

CLINICAL FEATURES

The clinical features of the cases of tuberculosis of the abdomen in Ibadan have been described.[9,11] Most of the patients presented with symptoms of progressive loss of weight associated with abdominal discomfort and pain in 90 per cent of cases and with diarrhea in 30 per cent of the cases.

Ascites occurred in about 60 per cent, and a palpable mass was felt in the abdomen in 40 per cent of the cases. The peripheral lymph nodes were palpable and provided means of making a histologic diagnosis in only 40 per cent of the cases, while the heaf test was unhelpful in 60 per cent of cases.

Laboratory investigations were unremarkable except for the moderate degree of anemia and the severe hypoproteinemia and hypocholesterolemia commonly found. Defect of absorption tests was found in about 30–35 per cent of cases with regards to the D. xylose test and the 3 day fecal fat estimations.

CHEST ROENTGENOGRAMS

Calcification. A total of 141 patients had at least 2 chest roentgenograms each. All of these had multiple minute calcifications in both hilar regions, situated most probably in the hilar lymph nodes. In addition, 29 of these had calcifications in each or both apices (Table 1).

Lymphadenopathy. Eleven patients had enlargement of the right hilar lymph nodes, in 3 of these there was bilateral paratracheal lymphadenopathy; 2 others had enlarged lymph nodes confined to the paratracheal regions; 6 of them also had enlarged lymph nodes on the left side (Fig. 1).

Pleural effusion. There were 14 cases of pleural effusion in either the left or right pleural cavities; 5 of these had bilateral pleural effusions. The effusions were basal

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and free except in 2 cases, where the effusions were apical with one on the left and the other on the right. Most effusions were moderate and occupied one-third to one-half of the respective thoracic cavity. In 3 cases, the effusions were massive, occupying the entire hemithorax. Twelve of these cases of pleural effusion also had associated ascites. In addition, there was a bronchopneumonic consolidation in 11 cases and a miliary pattern in 1 case (Table II).

Of the 55 patients with consolidations there were cavitations in 9 cases only. The cavities were unilocular, large and thick-walled; however, in 4 cases, all of which were in the upper lobes, they were multiple and small. The distribution of cavities in these 9 patients with consolidation is shown in Table III.

OTHER FINDINGS

Septal lines were shown at the bases in 2 cases without any other evidence of active lung or cardiac disease.

GASTROINTESTINAL TRACT

Pericardial effusions, as evidenced by enlarged hearts, triangular silhouettes on the erect posteroanterior roentgenograms, and proven at autopsy were seen in 3 cases.

Plain film roentgenograms. A total of 125 patients had plain film roentgenograms of the abdomen. The analysis of these roentgenograms demonstrated the following features (Table IV):

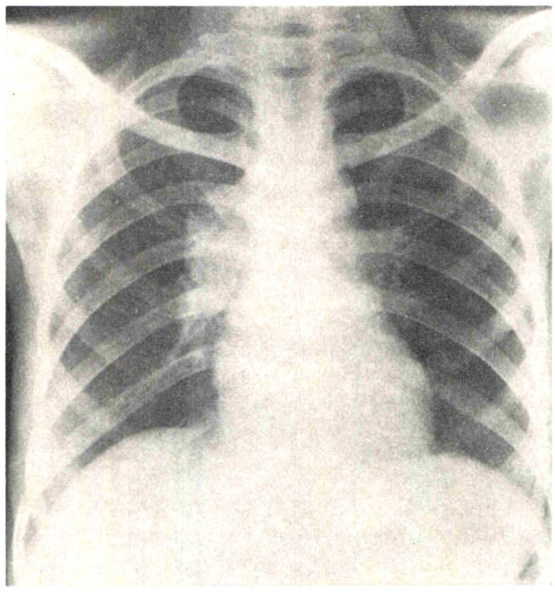

Fig. 1. Chest roentgenogram. A left hilar lymphadenopathy and bilateral hilar calcifications are seen.

Ascites. In 65 patients there were signs of ascites usually of moderate degree, but in 14 patients the ascites was extremely gross with concomitant dangerous diminution in thoracic capacity. Ascites was the commonest sign seen in this series and it occurred in 52 per cent of the cases (Fig. 2).

Gaseous distention. Generalized gaseous distention of the intestinal loops occurred in 35 cases (Fig. 3). Specific portions of dilatation that could be identified were as follows: stomach 3 cases (presenting as

Table I

CHANGES ON THE CHEST ROENTGENOGRAMS IN PATIENTS WITH TUBERCULOSIS OF THE ABDOMEN

	No. of Cases
Calcification in the chest	141
Tracheal or/and hilar lymphadenopathy	13
Pleural effusion	14
Consolidation/cavitations	55
Septal line	2
Pericardial effusion	3

Table II

DISTRIBUTION OF CONSOLIDATION IN THE LUNG FIELDS OF PATIENTS WITH TUBERCULOSIS OF THE ABDOMEN

	Right Lung No. of Cases	Left Lung No. of Cases	Bilateral Lesions
Upper lobes	15	7	2
Middle lobes	4	1	—
Lower lobes	26	26	10

TABLE III

DISTRIBUTION OF CAVITIES ON THE CHEST ROENTGENOGRAM OF PATIENTS WITH TUBERCULOUS ABDOMEN

	Right Lung	Left Lung	Bilateral
Upper lobe	6	5	3
Lower lobe	5	1	—

gastric outlet obstruction); jejunum 2 cases; and terminal ileum 12 cases (Fig. 3).

The pattern of gaseous distention was obstructive in 7 cases (1 case of ceco-colic intussusception and 6 cases of strictures in the terminal ileum); and paralytic in 2 cases with associated tuberculous peritonitis.

Right iliac fossa mass. There were 9 cases with signs indicating the presence of a mass in the right iliac fossa, due to tuberculous ileocolitis except for 1 due to appendicular abscess and another due to ceco-colic intussusception.

The triad of ascites, absence of gas shadow or gaslessness in the right iliac fossa (*i.e.*, the presence of a mass in the right iliac fossa), and segmental dilatation of the terminal ileum on plain film roentgenograms, in our experience, appears to be suspicious of intestinal tuberculosis.

Perforation. One case showed evidence of gross pneumoperitoneum on plain roentgenogram (Fig. 4). At autopsy this was found to be due to an obstructing annular hypertrophied type of tuberculosis of the ascending colon.

TABLE IV

CHANGES ON PLAIN FILM ROENTGENOGRAM OF THE ABDOMEN OF PATIENTS WITH TUBERCULOSIS OF THE ABDOMEN

	No. of Cases
Ascites	65
Gaseous distention	35
Right iliac fossa mass	9
Perforation	1
Calcifications	4
Hepatomegaly	5

Calcifications. Four patients showed evidence of calcifications in the abdomen. In 2 cases these were discrete and nodular and were in enlarged lymph nodes; in another case they were multiple and less discrete and in this case there was associated gross ascites. One case showed calcification within the lumen of the ileum—enterolith.

Enlargements of the liver and spleen. There was marked hepatomegaly in 9 patients, gross splenomegaly in 5, and gross hepatosplenomegaly in 4 cases.

CONTRAST MEDIUM STUDIES

BARIUM STUDIES

Barium swallow, meal and follow-through examinations were done on 89 patients: 31 patients had both barium meal and barium enema examinations. A routine

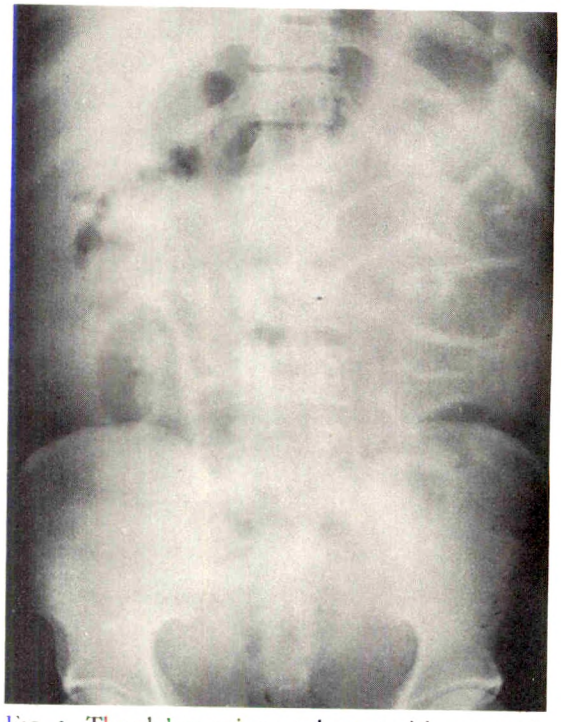

FIG. 2. The abdomen is protuberant with a ground-glass appearance and the bowel loops are centrally placed, indicating ascites. The cecal pole and ascending colon are not outlined by gas or feces.

follow-through roentgenogram was obtained a half-hour after the barium meal screening to show the small bowel. Of the 89 patients screened, 62 had abnormal studies and in 17 no abnormal findings could be seen. The abnormal findings in each region of the gastrointestinal tract were as follows:

Esophagus. One case showed a long stricture in the distal half of the esophagus studded with multiple intramural diverticula (Fig. 5, *A* and *B*).

Stomach. There were 2 cases with abnormal gastric lesions. One showed irregular narrowing of the antrum which was aperistaltic and with destroyed mucosa mimicking a carcinoma; the other demonstrated a large and deep ulceration on the lesser curvature of the stomach (Fig. 6). Both had changes also in the duodenum and small bowel.

Duodenum. Twenty-eight cases had abnormalities of the duodenum which can be classified into 3 types:

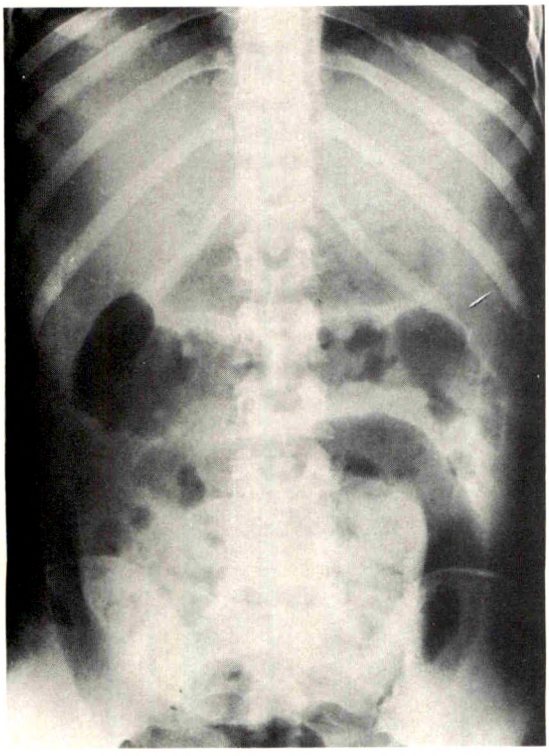

Fig. 3. There is segmental dilatation of the terminal ileum.

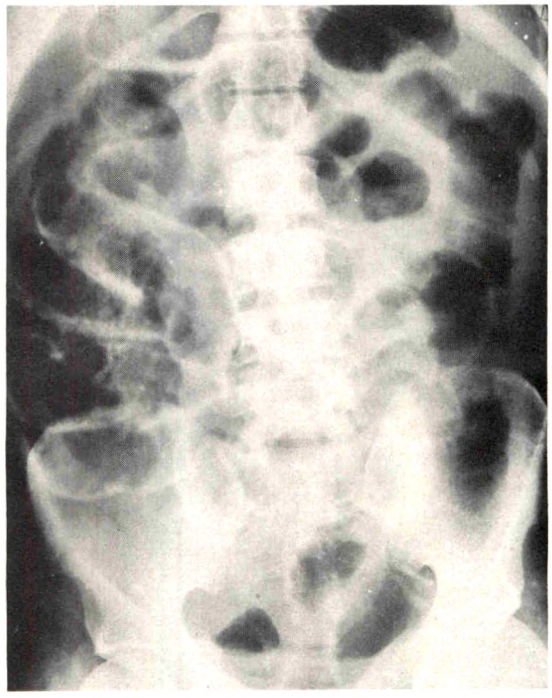

Fig. 4. Pneumoperitoneum. Free air is seen within the peritoneal cavity, and surrounding the bowel loops.

(a) Impressions. There were 19 cases with extrinsic filling defects due to enlarged lymph nodes on the medial aspect of the duodenal loop usually on the second and third portions of the duodenum mimicking carcinoma of the head of the pancreas (Fig. 7). Usually these had associated abnormal findings in the small intestine.

(b) Widening of the duodenal loop. In 5 cases the sweep of the duodenal loop was enlarged, and the loop widened without any filling defects or extrinsic impressions (Fig. 8). In 1, the stomach itself was displaced forwards and laterally.

(c) Obstruction of the duodenum. In 4 cases there was complete obstruction of the duodenum; 1 at the duodenojejunal flexure and 3 at the junction of the second and third parts of the duodenum (Fig. 9). These cases presented clinically as gastric outlet obstruction and the stomachs were distended.

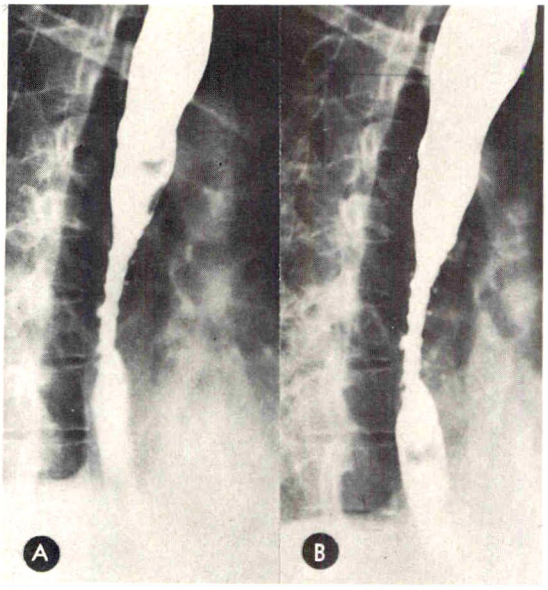

FIG. 5. (*A* and *B*) Esophagograms showing a long stricture in the middle third of the esophagus at the hilar level with intramural diverticulosis.

Jejunum and ileum. No specific small bowel enema studies had been done; and only micropaque had been used. However, the following changes were observed:

Disordered small bowel pattern. In 22 cases, there were signs of disordered small bowel pattern such as dilatation of the loops, dilution of the contrast medium, segmentation and marked slowness in transit through the small bowel. Fourteen of these cases also had multiple *Ascaris* worms; ova of *Strongyloides stercoralis* and *Giardia lambdia* were seen in the stool of 2 other cases.

However, certain other specific signs were observed in addition to the changes of disordered small bowel pattern:

(a) Segmental dilatation of bowel loops were observed in the duodenum (4 cases), jejunum (2 cases), ileum (1 case), and entire small bowel (19 cases).
(b) Strictures were usually multiple and commonly situated around the proximal jejunum and the terminal ileum (Fig. 10).

Other findings were: fixation of the loops in 7 cases; spiculation in 5 cases; fistulous communication between duodenum and transverse colon in 1 case.

Diagnostic pneumoperitoneum. In 1 patient with primary amenorrhea, and who had discrete nodular calcifications in the pelvis, a diagnostic pneumoperitoneum was attempted 4 times, and was unsuccessful on each occasion. At laparotomy, however, a plastic peritonitis was seen with the omentum studded with tubercles.

Barium enema examination. There were 50 patients studied with barium enema examinations and among these 26 showed abnormal findings. Most lesions were in the ileum and cecum, but no portion of the colon was exempt from involvement. The distribution of the sites of these 26 cases of tuberculous ileocolitis is shown in Figure 11. The lesions were mainly of 4 varieties:

(a) The *hyperplastic type* with a long segment of narrowing with rigidity and loss of distensibility—the so-called "pipe-stem colon" (Fig. 12). When this involved the cecum and terminal ileum, appearances were described as "the coned-cecum" (Fig. 13). The hyperplastic type was the commonest

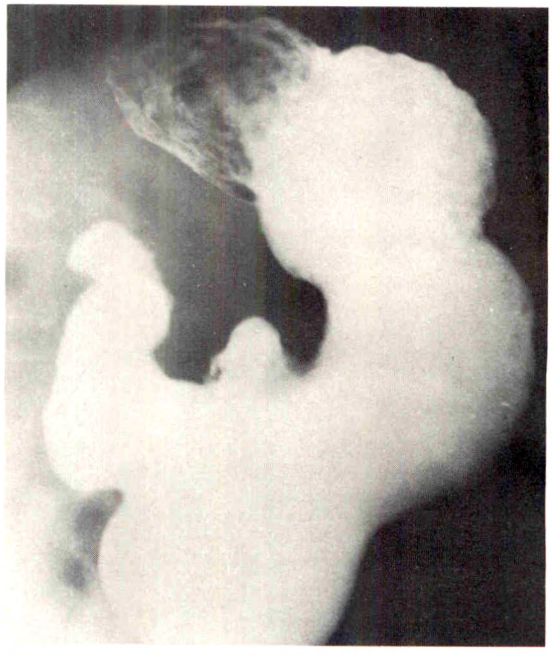

FIG. 6. An ulcer crater is shown in the lesser curvature aspect of the antrum. There is hold-up at the apex of the duodenal bulb.

type of colonic lesion found and this was usually in the ileocecal region (Fig. 14).

(b) *The ulcerative type* showed marked ulceration (Fig. 15).

(c) *The hyperplastic and ulcerative type* could co-exist to form the *mixed type.*

(d) *The carcinoma-like type* with a short annular filling defect and over-hanging edges was uncommon and occurred in only 3 cases, all of which were associated with the hyperplastic type.

(e) Other types included 2 cases of intussusception, 1 of appendicular mass and 2 of extensive colonic diverticulosis.

Most lesions were unifocal; however, multiple segmental lesions were also seen.

DISCUSSION

Tuberculosis is a very common disease in Ibadan. Although the lungs are by far the commonest organ involved, gastrointestinal tuberculosis does occur, but it is not as easily diagnosed as pulmonary tuberculosis.

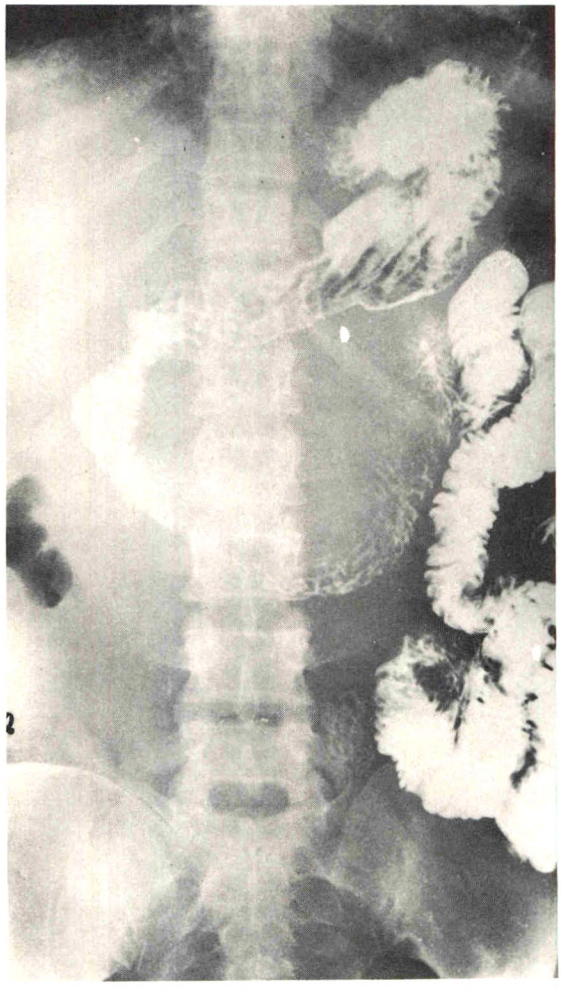

Fig. 8. Widening of the duodenal bulb with effacement of the mucosa on the medial aspect of the second and third parts of the duodenum. Ascites and right iliac fossa gaslessness are also shown.

Fig. 7. Marked impressions on the medial aspect of the second and third parts of the duodenum.

Even though only 160 patients were studied in this series, this number is an underestimation of the prevalence of the disease in this environment. A greater index of suspicion backed up by a more comprehensive diagnostic procedure, including radiologic studies such as barium studies, and other means of making a histologic or bacteriologic diagnosis is needed in order to reduce the number of the undiagnosed cases.

It is more often the advanced cases of intestinal tuberculosis that show roentgenologic changes;[3,12] therefore, as many of the

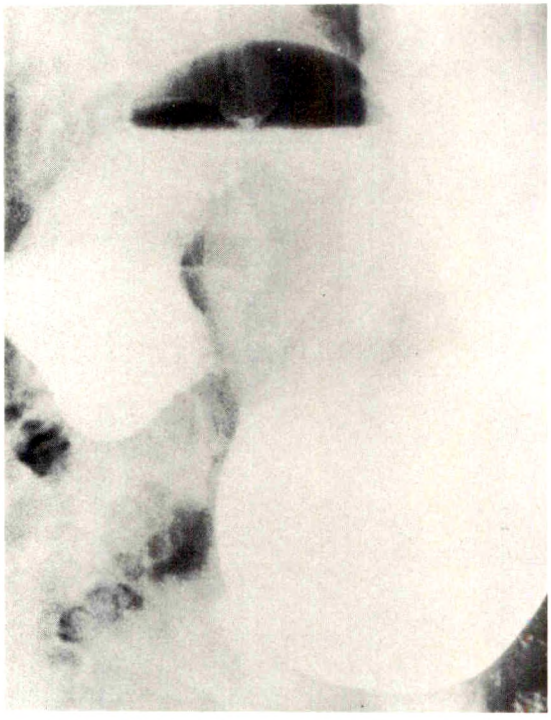

FIG. 9. Obstruction of the duodenum at the junction of its second and third parts.

cases seen at the Hospital were advanced cases, they showed various roentgenologic changes. It became apparent from this study that if the 3 standard examinations of the gastrointestinal tract (plain film abdominal roentgenography, barium meal, follow-through and barium enema examinations) were done, at least one of them could be highly suggestive of tuberculosis. It would, therefore, be necessary that all 3 standard examinations be scheduled and be carried out one after another until a positive diagnosis is obtained.

Fifty-two per cent of the cases showed roentgenologic evidence of ascites. Ascites is a recognized common clinical feature of tuberculosis of the abdomen. It should, therefore, provoke further bacteriologic and laboratory investigations.

The barium meal follow-through and barium enema examinations yielded highly suggestive changes in 79 per cent of cases, thus making these studies a very sensitive radiologic method in the diagnosis of abdominal tuberculosis. The chest roentgenogram is none the less important in this disease, which is believed to be secondary to pulmonary tuberculosis in this environment.[3] There are often roentgenologic changes of past or present pulmonary tuberculosis in almost every case. In this series there was evidence of present pulmonary disease in 27 cases.

PATHOPHYSIOLOGY OF THE ROENTGENOLOGIC FEATURES

The pathogenesis of tuberculosis of the gastrointestinal tract is generally believed to be due to the swallowing of a massive dose of tuberculous bacilli which later pass into the tubular glands of the intestinal mucosa where an inflammatory exudate is produced. The overlying mucosa may be cast off with the formation of the ulcer. The consequence of these mucosal ulcerations is either an attempt at healing by fibrosis or a spread. The bacilli may be carried from the submucosal lesions to the mesenteric lymph nodes which drain that segment of the bowel, thereby producing caseous lymph nodes with abscess formation. The other possible routes of infection of the gut are by hematogenous and/or lymphatic spread and also by direct spread from the serosa

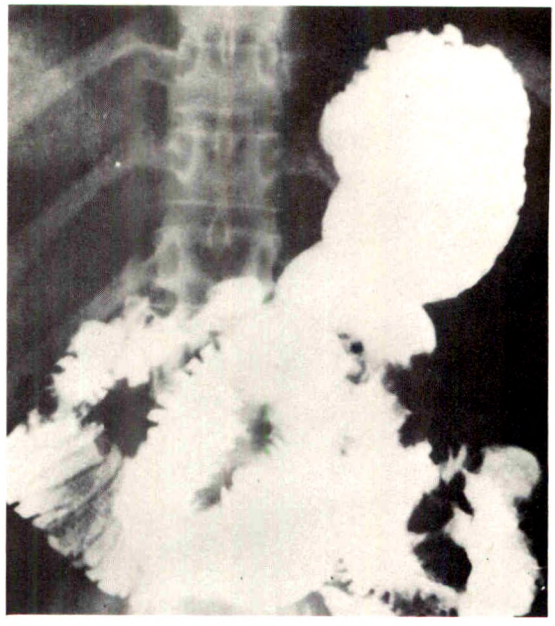

FIG. 10. Multiple strictures in the duodenum and jejunum (arrows).

by continuity from adjacent glands, or strictures.

These ulcers in the tubular glands could be seen roentgenologically as spiculations. The tuberculous ulcers may later become confluent to form the classical "girdle ulcer" with undermined edges. This manifests radiologically as a "napkin-ring" filling defect which mimics a carcinoma radiologically. Occasionally, the mucosa is completely denuded as in the "pipe-stem colon."

Healing by fibrosis gives rise to the strictures seen in the small bowel, and the hyperplastic types of tuberculosis seen in the cecum and colon. Shortening and narrowing also result from the process of fibrosis and gives rise to such features as the contracted cecum with its "coned" appearance, the strictures and the stretching of the terminal ileum with the increased angulation between it and the cecum, the so-called "goose-neck" deformity,[3] and the fibrosis of the ileocecal valves with resultant ileocecal incompetence.

The involvement of the intraabdominal and mesenteric lymph nodes could be demonstrated roentgenologically by lymphangiography.[20] Such enlarged lymph nodes would produce extrinsic impressions on the intestine, such as on the pyloric antrum, inner aspect of the duodenal loop and the small intestine. Ascites and the malabsorption syndrome, especially coarsening of the mucosa due to edema, are most often a direct result of lymphatic obstruction from the enlarged mesenteric lymph nodes.

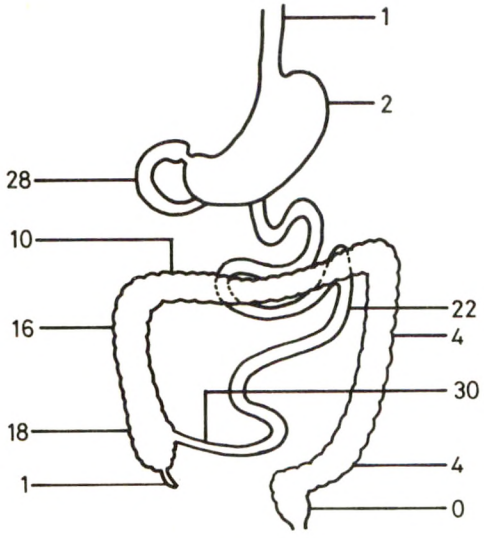

Fig. 11. Diagram showing the distribution of lesions in the gastrointestinal tract as demonstrated radiologically.

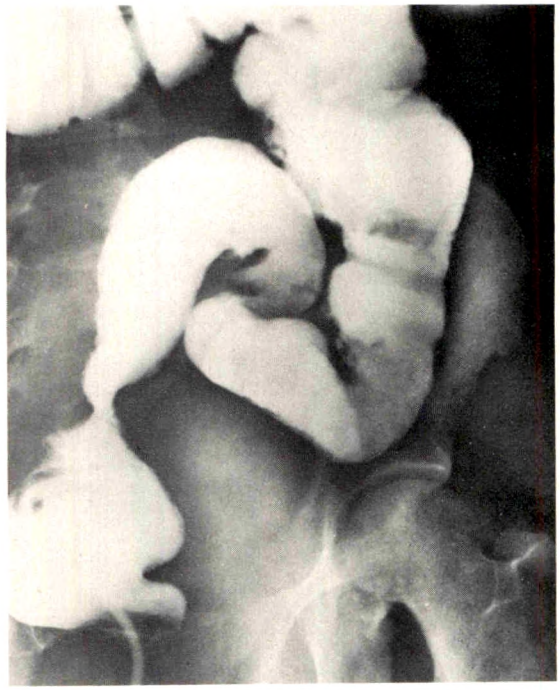

Fig. 12. The "pipe-stem" appearance. There is a smooth long stricture in the rectosigmoid region.

Occasionally, the lymph nodes become caseous and matted together to form masses which produce widening of the duodenal loop, obstruction of the duodenum, or the appendix mass with appendicular abscess.

Peritonitis is a result of involvement of the serous cavity with tubercle bacilli either by direct extension, or by hematogenous or lymphatic spread. There are 2 varieties; the wet with ascites; and the dry with caseous nodules and adhesions forming the so-called "plastic" abdomen.

The distribution of lesions in the gastrointestinal tract is shown in Figure 14. The lesions in the large bowel were demonstrated by barium enema examinations, whereas those in the terminal ileum were by both barium enema in 15 cases and barium meal follow-through examinations

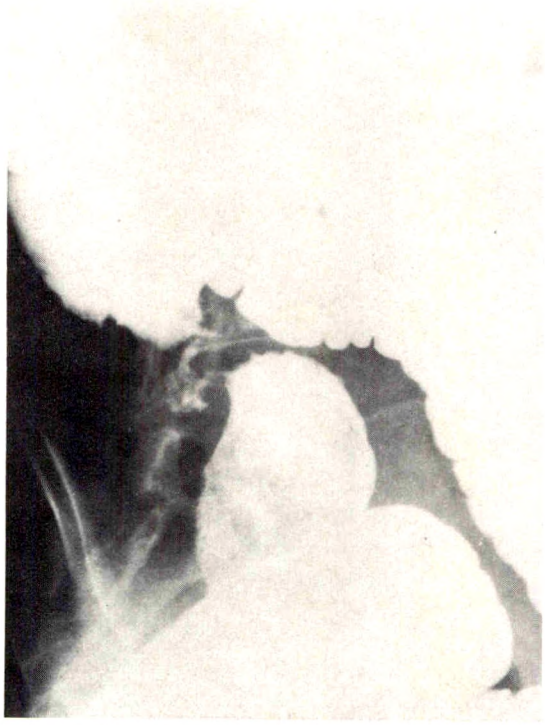

FIG. 13. The "coned" cecum. The cecal pole is contracted into a cone. The terminal ileum shows proximal dilatation with a stricture in its distal (cecal) end.

in 22 cases. Seven cases had both examinations performed.

Esophageal tuberculosis is rare. Only 3 cases were reported in a series of 117 cases of tuberculosis of the gastrointestinal tract.[19] These 3 cases showed smooth stricture in the mid-third of the esophagus due to direct spread of the enlarged tracheobronchial lymph nodes. Only 1 case is hereby reported, but in this patient, there was no evidence of enlarged lymph nodes. This case is also unique in that it is the only case of esophageal intramural diverticulosis due to tuberculosis reported in the literature. Intramural diverticulosis of the esophagus as such is rare. Only 7 cases have been reported in the literature[13] and only in 2 was the intramural diverticulosis limited to the area of stricture.[13,18] These strictures were due to segmental muscular hypertrophy and reflux esophagitis, respectively. Intramural esophageal diverticulosis has also been associated with moniliasis[17] and chronic inflammatory changes.[21] The formation of diverticulosis is most probably due to extension of the mucosal ulcers into the muscularis layer. A case of tuberculous diverticulosis of the colon was reported by us in an earlier series of tuberculous ileocolitis.[12] The pattern of diverticulosis in these cases is reminiscent of tuberculous salpingitis—the so-called "salpingitis isthmica nodosa."

Tuberculosis of the stomach and duodenum is very rare even in patients with pulmonary or intestinal disease, the incidence being 0.3–2.3 per cent.[8,10,16] In our series gastroduodenal lesions accounted for 18 per cent.

The rarity of lesions in the stomach and duodenum may be due to: sparsity of lymphoid tissue in the stomach; intact gastric mucosa; acidity of the stomach; and the rapidity of passage of the ingested organism through the stomach.[5,7,14]

The high incidence of lesions in the duodenojejunal and also in the ileocecal region appears to be in keeping with the presence of lymphatic nodes in these regions.

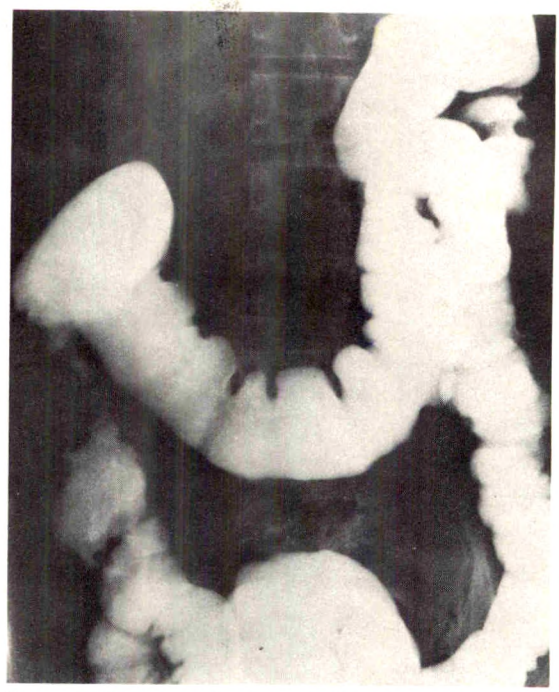

FIG. 14. The hyperplastic type. The ascending colon and cecum show multiple filling defects. There is dilatation of the terminal ileum.

Ulcerative lesions of the stomach or duodenum are less commonly demonstrable roentgenologically than hypertrophied lesions.[4,11] In this series 1 case showed a large antral ulcer and other hypertrophied changes as well as impressions due to enlarged lymph nodes. The case of antral ulcer would have been difficult to differentiate from malignant peptic ulceration without a classical tuberculous lesion in the lungs.

In 4 cases reported by Balikian *et al.*[4] the lesions were primarily localized at the pyloroduodenal area, but our cases and those of Werbeloff *et al.*[19] were not localized to those regions, but in fact involved the stomach, the duodenum and the small bowel.

No case of associated carcinoma was noted even though Palmer[15] claimed that 10 per cent of cases of gastric tuberculosis coexisted with gastric carcinoma.

The duodenal lesions may mimic carcinoma of the pancreas or a lymphomatous infiltration of the gastroduodenal region. The various appearances of the duodenum included: extrinsic impressions; widening of the loops; strictures and obstruction of the duodenal lumen due mainly to compression from the markedly enlarged lymph nodes; and possibly also from serosal involvement. It is interesting to note that Werbeloff *et al.*[19] also reported 3 cases of pyloroduodenal obstruction in the African patients.

In our environment, barium studies showing a malabsorption or disordered small bowel pattern may be due to the presence of an overload of intestinal parasites. However, fixation of the bowel loops on supine and erect roentgenograms, spiculation and the presence of multiple strictures in the small bowel are signs which together are highly suggestive of tuberculosis of the abdomen: and when these signs are added to those of the plain film roentgenograms showing a triad of ascites, right iliac fossa gaslessness and dilatation of terminal ileum, a diagnosis of abdominal tuberculosis is almost certain in this environment.

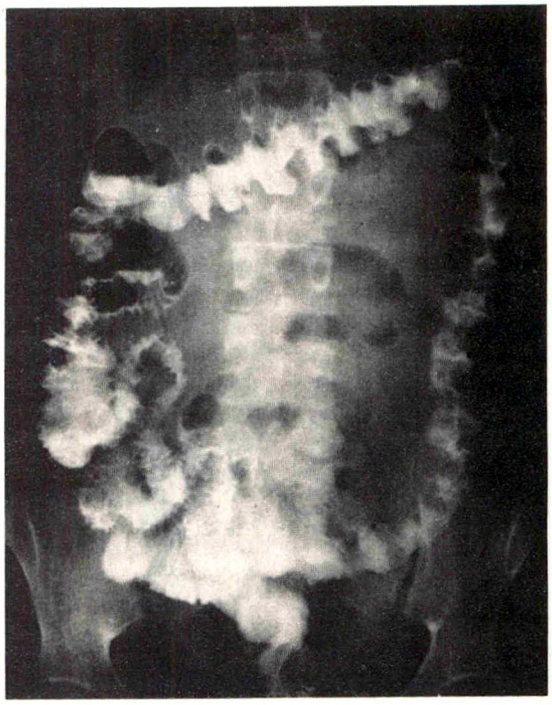

Fig. 15. The ulcerative type. There are marked spiculations of the ascending colon, the cecum and the terminal ileum.

The distribution of lesions in the large bowel supports previous views that the ileocecal region is the commonest site of involvement.[1,2] Distal lesions in the left side of the colon previously thought to be rare have been reported,[12] and are again shown in this series. No rectal lesions have been observed.

The lesions are usually hyperplastic, ulcerative of mixed, but the hyperplastic type is the commonest type and it usually involves several anatomic regions of the colon continuously, especially the terminal ileum, the cecum and the ascending colon. This occurred in 15 out of 26 cases. The so-called "coned cecum" thought to be pathognomonic of amebiasis occurred twice in this series.

The rarer forms of tuberculous colitis, such as the multiple or segmental lesions, the pipe-stem colon, diverticulosis and enteroliths have been reported earlier.[12]

SUMMARY

The roentgenologic features of 160 cases

of tuberculosis of the abdomen are reviewed.

The 3 standard examinations of the gastrointestinal tract (plain film abdominal roentgenography, barium meal and follow-through studies, and barium enema examinations) are required to provide useful pointers towards the diagnosis.

In plain film roentgenography of the abdomen, the triad of ascites, absence of gas shadows in the right iliac fossa, and segmental dilatation of the terminal ileum demonstrates features which are very suspicious of intestinal tuberculosis.

In the barium meal studies showing disordered small bowel patterns, tuberculosis of the abdomen should be considered when this pattern is associated with fixation of bowel loops on supine and erect roentgenograms, spiculation and the presence of multiple strictures in the small bowel.

Although the duodenojejunal and ileocecal regions are the commonest sites involved, lesions are not confined to these sites alone, but may also involve any part of the alimentary canal such as the esophagus and the small and large bowel. However, no anorectal lesions were encountered in this study.

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VOL. 123, NO. 2

RETROGRADE PANCREATOGRAPHY IN AUTOPSY SPECIMENS*

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SELENOMETHIONINE scanning, hypotonic duodenography, and selective arteriography are procedures that have been used with only limited success in the study of the pancreas. With the advent of fiberoptic technology and the development of the flexible fiberoptic duodenoscope, endoscopic pancreatography has proved to be a feasible procedure.[12,13,15,16] Experienced endoscopists can cannulate the papilla of Vater in up to 90 per cent of patients.[11]

To aid in the interpretation of the pancreatogram, knowledge of the anatomic and pathologic appearance of the pancreatic region, as well as its correlation with clinical findings, is essential. In an attempt to gather data to this end, we studied 55 pancreatic specimens by means of retrograde pancreatography.

MATERIAL AND METHOD

The main pancreatic duct was opacified via the papilla of Vater in 55 autopsy cases (the ages of the patients ranged from 17 days to 91 years). In 7 additional cases, dissection was carried out for anatomic study only. Three pancreatograms were obtained *in situ*, and the remainder were done after *en bloc* removal of the stomach, duodenum, and pancreas. The contrast medium (50 per cent Hypaque) was hand-injected, 2 to 5 ml. usually sufficing to opacify the entire pancreatic duct system in adult specimens. *In situ*, more than 35 ml. were required if the common bile duct, cystic duct, gallbladder, and intrahepatic radicles were opacified along with the pancreatic ducts (Fig. 1). After roentgenographic exposures, the specimens were dissected. The relationships of the common bile duct, main and accessory pancreatic ducts, and the major and minor duodenal papillae were studied in each case, and sections were taken for microscopic examination. Clinical data were available in every case.

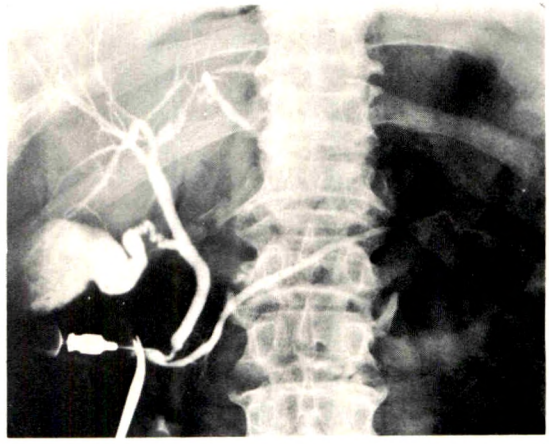

FIG. 1. Normal retrograde pancreatocholangiogram obtained *in situ* at autopsy. Common bile duct and pancreatic duct join to form a well-defined ampulla of Vater before opening into duodenum.

RESULTS

In most cases, the common bile duct and the main pancreatic duct opened together at the papilla of Vater, either having an interposed septum or being joined (Fig. 1). This was true in 87 per cent (54 of 62) of cases in our series. In the remaining 8 cases, the two ducts opened at a distance, usually 2 to 3 cm. apart. In 6 of these 8 cases, the main pancreatic duct opened at the minor duodenal papilla, proximal to the opening for the common bile duct at the papilla of Vater (Fig. 2, *A* and *B*), and in 2 cases, the main pancreatic duct opened distal to the opening for the common bile duct (Fig. 2*C*).

The accessory pancreatic duct was opacified in 57 cases, and opened independently into the duodenum in 12 of these 57 cases (21 per cent) (Fig. 3*A*). An ampullary dila-

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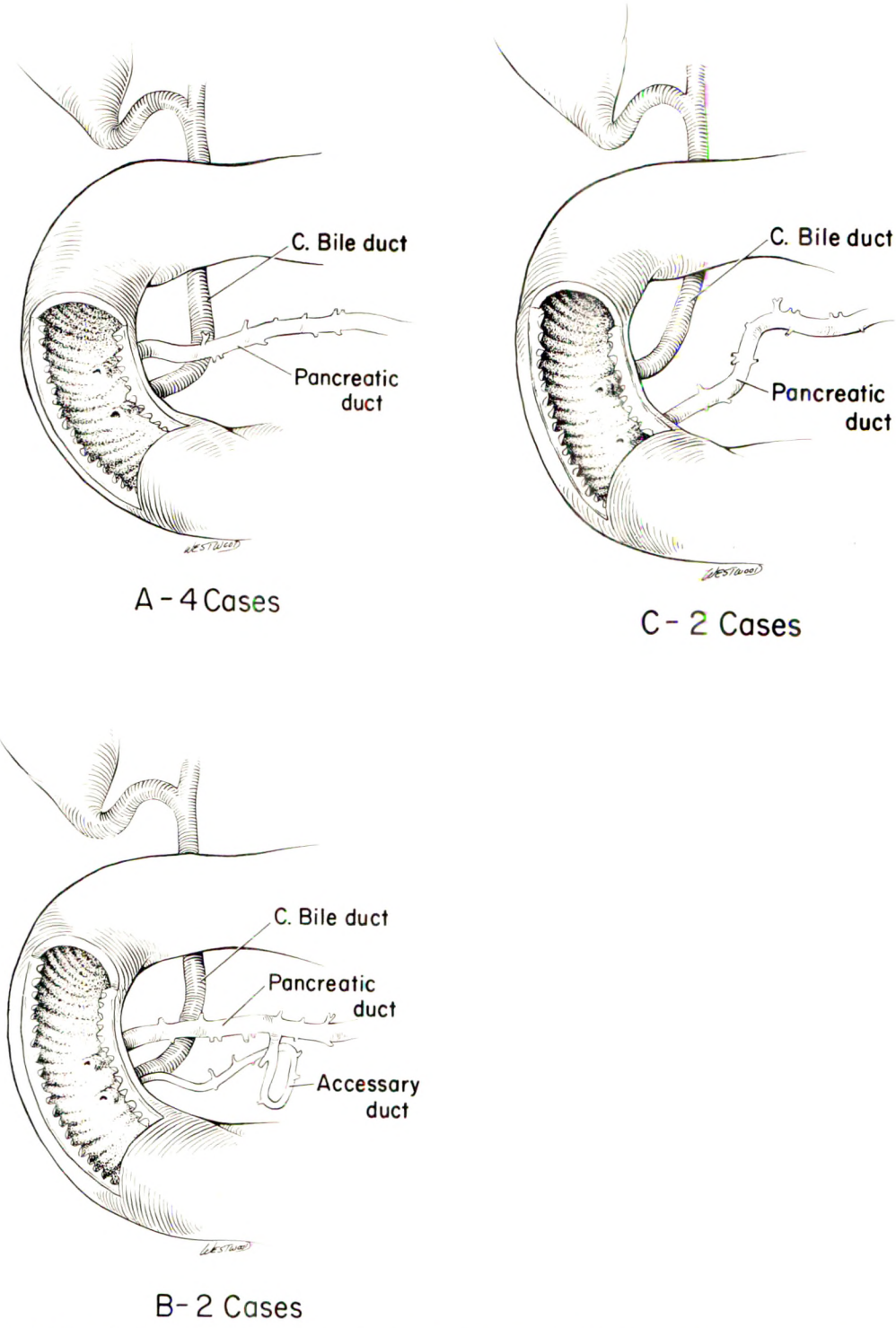

FIG. 2. Schematic representations of 8 cases in which common bile duct and main pancreatic duct had separate orifices. (*A*) Main pancreatic duct opens at minor duodenal papilla, and common bile duct opens at major duodenal papilla (papilla of Vater). (*B*) Accessory pancreatic duct joins common bile duct to open at major duodenal papilla. Main pancreatic duct opens at minor duodenal papilla. (*C*) Common bile duct opens at minor duodenal papilla, and main pancreatic duct opens at the papilla of Vater.

tation was identified at the end of the accessory pancreatic duct in 8 of the 57 cases (14 per cent). In 2 of the 8 cases, the accessory duct had a patent orifice at the minor duodenal papilla, and the ampulla was located immediately adjacent to the papilla. In the remaining 6 cases, the accessory duct ended in a blind pouch within the pancreatic parenchyma (Fig. 3*B*).

The ampulla of Vater, defined as a pouch-like dilatation at the junction of the common bile duct and main pancreatic duct, was an inconstant structure, well formed in only 4 of the 62 cases (6 per cent) (Fig. 1). In the remaining 58 cases, the main pancreatic and common bile ducts generally tapered significantly, as they traversed the muscularis of the duodenum.

The main pancreatic duct tapered gradually toward the tail, but generally there were undulations and smooth irregularities. The main pancreatic duct was most often widest near the point of juncture with the accessory pancreatic duct, in the head of the pancreas, 1 to 4 cm. from the duodenum.

The average maximal diameter of the main pancreatic duct increased with patient age, being 3.3 mm. in the age group from 31 to 50 years (9 patients), 3.5 mm. from 51 to 70 years (13 patients), and 4.6 mm. from 71 to 90 years (10 patients). The largest diameter (1 cm.) of a normal pancreatic duct was seen in a 91 year old woman. She had no known history of pancreatic disease, and histologically, her pancreas was normal. The size of the pancreatic duct was not related to sex. The length of the adult main pancreatic duct ranged from 15 to 21 cm.

Pancreatograms were obtained in 2 cases of primary carcinoma: one lesion was located in the head of the pancreas and the other in the tail. The pancreatic duct was dilated behind the carcinoma in the head of the pancreas. In both cases, the tumors were undifferentiated adenocarcinomas, and there was extravasation of contrast medium into the mass (Fig. 4, *A* and *B*).

Extravasation also occurred in a third case, in which the tail of the pancreas was involved with a necrotic lymphoma arising in the hilum of the spleen (Fig. 5*A*). In a fourth case, there was extravasation into the head and body of the pancreas, where abscess formation had occurred (Fig. 5*B*).

In 3 cases in our series, there were histologic alterations indicative of chronic pancreatitis. Pancreatograms in 2 of these cases showed irregularities of the ducts, with areas of stricture, and saccular ectasia of the secondary ducts (Fig. 6*A*). The

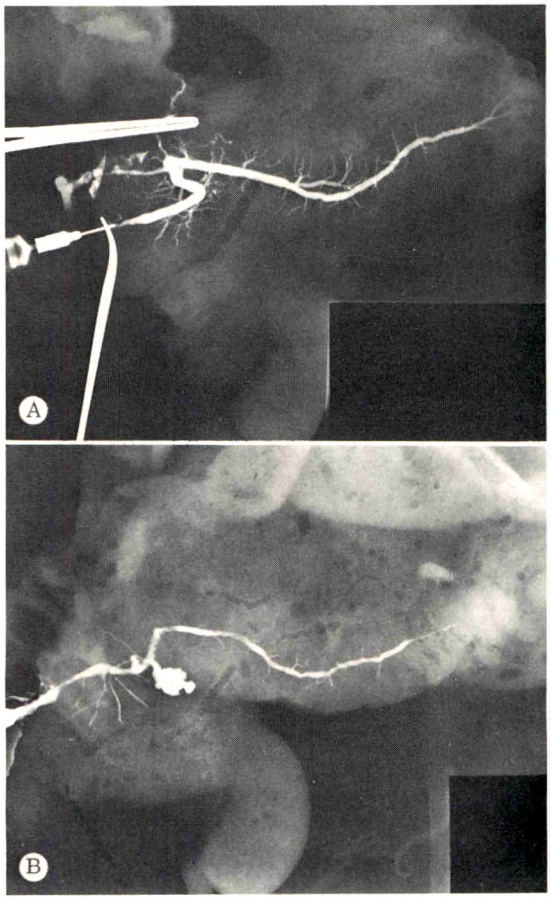

Fig. 3. (*A*) Separate orifices for main and accessory pancreatic ducts. Contrast medium injected through major duodenal papilla exits via accessory pancreatic duct into duodenum through pinhole opening at minor duodenal papilla. (*B*) Large blind pouch at end of accessory pancreatic duct. Ampullary dilatations are more common at end of accessory pancreatic duct than at junction of main pancreatic and common bile ducts (ampulla of Vater).

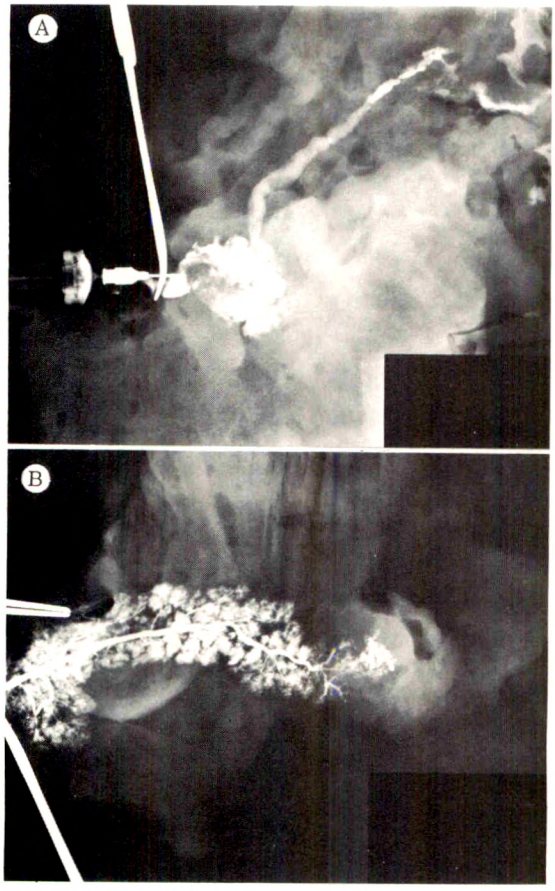

FIG. 4. (*A*) Undifferentiated adenocarcinoma of head of pancreas. Extravasation into mass. Pancreatic duct is dilated behind tumor. (*B*) Diffuse opacification of pancreatic parenchyma from autolysis. Main pancreatic duct is attenuated abruptly at site of carcinoma arising in tail of pancreas. Extravasation into tumor.

third pancreatogram showed no abnormality.

Obvious saccular ectasia of secondary ducts was demonstrated on 5 pancreatograms (Fig. 6), including 2 of the cases of pancreatitis. In 3 of these cases, squamous metaplasia of ductal epithelium was found microscopically after sectioning of random specimens (Fig. 7, *A* and *B*; and Table 1). One of the 2 specimens that showed no squamous metaplasia was so extensively involved with pancreatitis that no epithelium could be identified. Squamous metaplasia also was found in the third case of chronic pancreatitis, in which the pancreatographic findings were normal and there was no ductal ectasia. In this case, however, there was no clinical history of pancreatitis, and the histologic changes were minimal. Squamous metaplasia was not a feature of the pancreases that were without ductal ectasia and in which other microscopic changes of pancreatitis were absent.

Two cases showed microscopic evidence of acute pancreatitis, and in both of these, pancreatograms showed dense, fluffy, diffuse opacification of the pancreatic parenchyma (Fig. 8). A third case, with massive infarction of the pancreas, also showed dense parenchymal opacification. Parenchymal opacification also was readily pro-

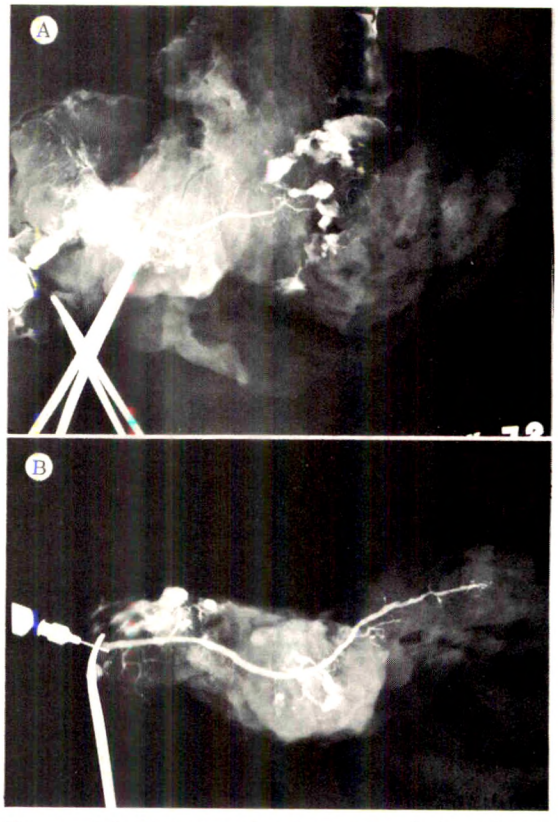

FIG. 5. (*A*) Extravasation into necrotic lymphoma involving tail of pancreas and hilum of spleen. Opacification of parenchyma in head of pancreas due to autolysis. (*B*) Suppurative pancreatitis. Extravasation of contrast medium into 2 areas of abscess formation, one in head and one in body of pancreas.

duced by injecting the contrast medium under high pressure and overfilling the duct system. Such opacification also was often seen in pancreases that had begun to undergo autolysis (Fig. 4*B*; and 5*A*).

DISCUSSION

Many anatomists have studied the pancreas and its relationship to the common bile duct and the duodenum since the original observations of Hoffman (1641), Wirsung (1642), Bidloo (1685), and Santorini (1775). Still, a surprising amount of confusion exists, owing largely to differences in methods, descriptive terms, and concepts. The anatomic variations can be understood, and much of the confusion dispelled, by an understanding of the embryologic development.

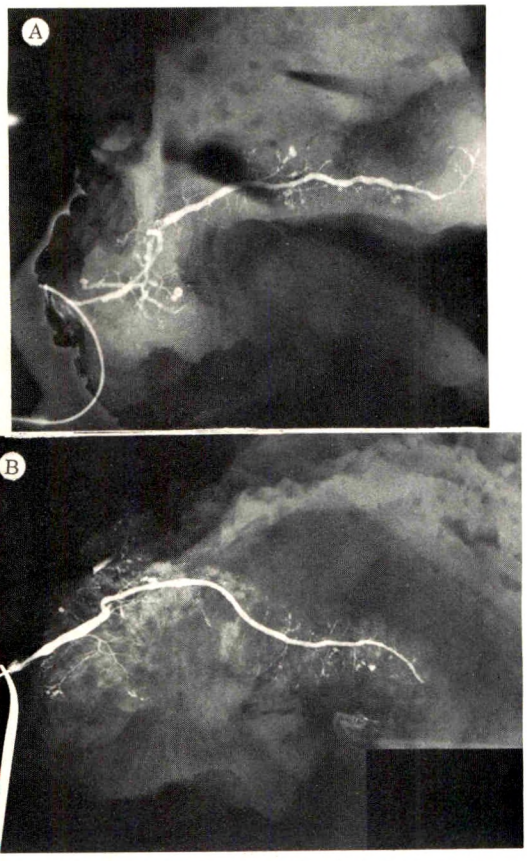

Fig. 6. (*A*) Chronic pancreatitis. Well-developed saccular ectasia of secondary pancreatic ducts. Irregularities of main pancreatic duct with stricture at junction of main and accessory pancreatic ducts. (*B*) Saccular ectasia of secondary pancreatic ducts. Squamous metaplasia of ductal epithelium present microscopically. No clinical or histologic evidence of chronic pancreatitis.

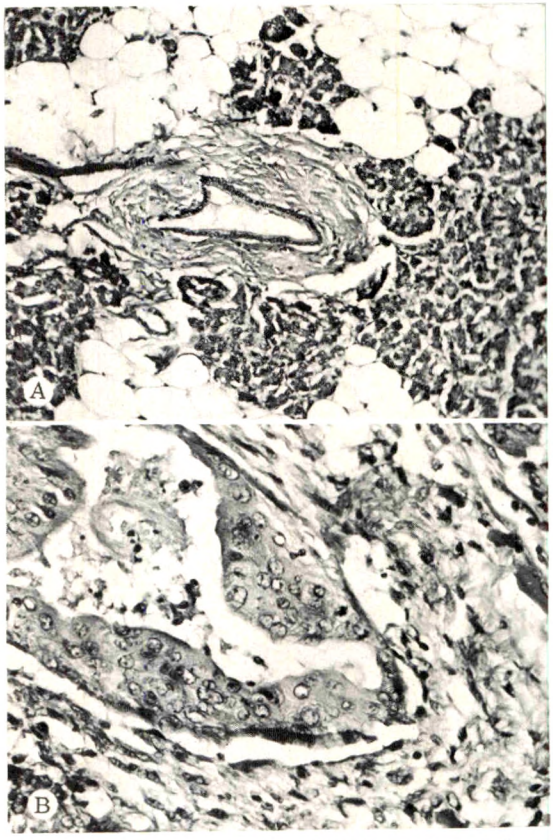

Fig. 7. (*A*) Normal pancreatic ductule. Low columnar epithelium. (Hematoxylin and eosin; ×160.) (*B*) Well-developed squamous metaplasia of ductal epithelium. Patient had chronic relapsing pancreatitis. Saccular ectasia of secondary pancreatic ducts on pancreatogram. (Hematoxylin and eosin; ×400.)

The pancreas develops from two endodermal anlagen, each with a separate central duct. The first arises as an outpouching from the dorsal wall of the primitive gut tube and is called the "dorsal pancreas." It grows more rapidly than its counterpart and elongates to eventually form the tail and body of the pancreas and a small anterior portion of the head of the pancreas. The second endodermal anlage develops from the ventral wall of the primitive gut tube and is called the "ventral pancreas." It migrates away from the duodenum with

TABLE I

RELATIONSHIP OF DUCTAL ECTASIA AND SQUAMOUS METAPLASIA OF DUCTAL EPITHELIUM

Age (yr.)	Obvious Ectasia of Secondary Ducts	Squamous Metaplasia
76	1	Absent
71	2	Present
70	3*	Present
72	4	Present
53	5*	Absent†

* Pancreatitis.
† Epithelium destroyed.

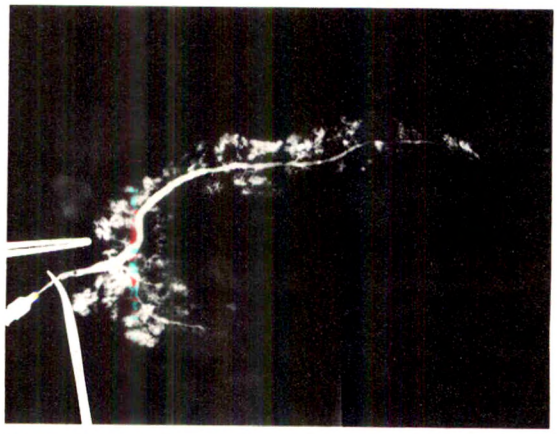

FIG. 8. Diffuse parenchymal opacification. Present in acute pancreatitis, in pancreatic infarction, and in overfilling of pancreatic ducts by vigorous injection. Commonly seen at autopsy in presence of autolysis.

the developing common bile duct. Unequal growth of the duodenal walls causes the common bile duct and its attached ventral pancreas to migrate into the dorsal mesentery, where the dorsal and ventral pancreases then become fused. The ventral pancreas gives rise to the bulk of the head of the pancreas, including the uncinate process.[2]

The duct of Wirsung is composed of the entire duct derived from the smaller ventral pancreas, plus the lateral two-thirds of the duct of the dorsal pancreas, which drains the body and tail. It most commonly joins the common bile duct and empties into the duodenum at the major duodenal papilla (of Vater). The remaining portion of the duct of the dorsal pancreas, draining a small anterior portion of the head of the pancreas, forms the duct of Santorini, which in a few cases retains its independent opening into the duodenum at the minor duodenal papilla, 1 to 3 cm. proximal to the major duodenal papilla.

The duct of Wirsung is the more important vessel for transport of pancreatic exocrine secretions into the duodenum in most cases and is generally referred to as the "main pancreatic duct." The duct of Santorini usually serves as an accessory pancreatic duct and is generally so named. In a few cases, the portion of the duct of Wirsung that derives from the ventral pancreatic anlage, that is, the medial one-third, remains underdeveloped. The duct of Santorini then becomes large and acts as the dominant purveyor of pancreatic juices. Functionally and anatomically, under these circumstances, the duct derived from the dorsal pancreatic anlage, whose medial portion is the duct of Santorini, is the main pancreatic duct. This is one mechanism by which the biliary and pancreatic systems attain independent drainage into the duodenum.

In another few patients, the dorsal and ventral anlagen fail to unite, and two independent glands develop, each with its own duct system. The dorsal pancreas is considerably larger; and its duct is the main pancreatic duct and it opens independent of the common bile duct. In describing the anatomy of the cases in our series, we have used the term "main pancreatic duct" to refer to whichever duct was anatomically larger, and therefore functionally predominant, regardless of its embryologic origin.

Failure of the ventral anlage to migrate away from the duodenum with the developing common bile duct is another mechanism by which the main pancreatic duct and common bile duct develop separate openings into the duodenum. Incomplete migration results in a septum being inter-

posed between the pancreatic and common bile ducts, which then share the papilla of Vater. This common anatomic arrangement explains some of the failures to opacify both the pancreatic and the biliary duct systems after cannulation, even though only one opening in the duodenum is identified.

Obstruction of the pancreatic duct by carcinoma is well known[7,8,11] and not surprising since the vast majority of pancreatic carcinomas arise from ductal epithelium. Strictures and dilatations of the main pancreatic duct are findings in chronic pancreatitis previously demonstrated on both the operative and the endoscopic pancreatogram.[7,10,11,14] The distinction between obstruction by tumor and benign stricture may be difficult. However, presence of multiple strictures and intraductal calculi indicates chronicity and therefore benignancy, even though there is evidence that patients with chronic pancreatitis have a predisposition to develop pancreatic carcinoma.[1]

Histologic features of chronic pancreatitis include, in addition to intraductal calculi, chronic inflammatory cell infiltrate, variable amounts of fibrosis, and squamous metaplasia of ductal epithelium. Squamous metaplasia is common in well-established, chronic, relapsing pancreatitis. However, its occurrence in pancreases with no other microscopic evidence of pancreatitis, in patients with no clinical history of pancreatitis but in whom evidence of saccular ectasia of secondary pancreatic ducts is seen on the pancreatogram, is an unexpected finding, first described by Birnstingl[3] in 1959. Its significance is not known, but it may represent a ductal reparative phenomenon in response to low-grade chronic injury or irritation. The frequency of saccular ectasia in our series (9 per cent) suggests the possibility of a high incidence of what might be called "subclinical pancreatitis" in the general population. The normal ampulla, which commonly is located at the end of the accessory pancreatic duct, should not be mistaken for the saccular ectasia that occurs in association with squamous metaplasia of ductal epithelium.

Diffuse opacification of pancreatic parenchyma in acute pancreatitis has been reported by others.[4,5,8,10,11,17] The mechanism appears to be an alteration in cell membrane permeability after injury, and this accounts for its occurrence in infarction and autolysis. When the parenchyma is opacified, trypsin (instead of trypsinogen) is found in the pancreatic juice.[6] Parenchymal opacification as a result of vigorous injection is noteworthy, since this is a definite hazard during *in vivo* pancreatography. The appearance of parenchymal opacification during endoscopic pancreatography is uniformly associated with an elevated serum amylase level,[4,5,9–11] and the clinical diagnosis of acute pancreatitis generally is a contraindication for the procedure.

SUMMARY

Sixty-two pancreases were dissected at autopsy. In 55 of them, the pancreatic ducts were filled with 50 per cent Hypaque and roentgenograms were made prior to dissection. Clinical information (available in every case) was correlated with the gross and microscopic findings and findings on the pancreatograms.

The anatomically and functionally predominant duct was considered the "main pancreatic duct" regardless of its embryologic development. The common bile and main pancreatic duct opened independently into the duodenum in 8 of the 62 cases (13 per cent). The accessory pancreatic duct had a patent orifice into the duodenum in 12 of 57 cases (21 per cent). The ampulla of Vater was well developed in only 4 of the 62 cases (6 per cent), but an ampullary dilatation was present twice as often at the end of the accessory pancreatic duct, in both those that ended blindly and those that opened into the duodenum. The orifices for the accessory

duct were often tiny pinhole openings.

There were 2 primary carcinomas of the pancreas, one in the head and one in the tail. The pancreatic duct was almost completely obstructed in each case. Both tumors were undifferentiated adenocarcinomas, and extravasation occurred into each one of them. Extravasation also occurred into a necrotic lymphoma involving the tail of the pancreas, and into two areas of abscess formation in another case.

Diffuse, dense, fluffy opacification of pancreatic parenchyma, due to alteration in cell membrane permeability, was demonstrated in acute pancreatitis, infarction, autolysis, and overfilling of the ducts by vigorous injection.

Three pancreases showed microscopic changes of chronic pancreatitis. The pancreatogram on one was normal, but the microscopic changes were minimal, and pancreatitis was not suspected clinically. The other 2 cases were symptomatic, and their pancreatograms showed strictures and irregularities of the main pancreatic duct as well as saccular ectasia of the secondary ducts. Saccular ectasia was present in three additional pancreases, two of which showed squamous metaplasia of ductal epithelium without other microscopic stigmata of chronic pancreatitis and no clinical features to suggest pancreatitis. The possibilities exist that ectasia of secondary ducts and squamous metaplasia of ductal epithelium are manifestations of low-grade injury and that "subclinical pancreatitis" may be common in the general population.

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VOL. 123, NO. 2

PREOPERATIVE ANGIOGRAPHIC LOCALIZATION OF INSULIN-PRODUCING TUMORS OF THE PANCREAS*

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SEVERAL types of islet-cell tumors of the pancreas produce various hormones,[2,20] and much has been written concerning the diagnosis and localization of the different types of islet-cell tumors. The accuracy of angiographic diagnosis and localization of insulin-producing tumors ranges from 20 to 90 per cent. Because of inadequate preoperative studies, 15 to 30 per cent of explorations for islet-cell tumors require a second operation.[18,19] The final result in many patients is a blind partial or subtotal pancreatectomy, because early statistics have suggested that this is the most beneficial procedure.[19] This recommendation has since been reviewed,[17] and one author[18] even suggests that blindly resecting the head of the pancreas may be a more beneficial procedure. To date, only 3 of the approximately 100 angiographically demonstrated tumors reported in the literature could not be palpated at surgery.[1,6] The high incidence of second operations and partial pancreatic resections suggests that many other tumors are not palpable by the surgeon.

The authors reviewed their experience with a series of clinically documented insulin-producing islet-cell tumors that were referred for angiographic localization.

MATERIAL AND METHOD

Between January 1969 and July 1974, 25 patients were operated upon for the diagnosis of insulin-producing islet-cell tumors. Of the 25, 22 had preoperative angiography done to localize the pancreatic tumor; 2 additional patients also underwent angiography for the same purpose; one of these was not operated on because the angiographic findings were negative, and in the other, they were false-positive. Thus, 24 patients undergoing angiography form the basis for this report.

Prior to referral, each case satisfied Whipple's triad: (1) symptoms of hypoglycemia provoked by fasting; (2) blood glucose level at or below 40 mg./dl. at the time of symptoms; and (3) relief of symptoms of hypoglycemia after the administration of glucose. All patients had one or more confirmatory laboratory test results: (1) prolonged fasting; (2) intravenous tolbutamide test; or (3) elevated plasma insulin levels by radioimmunoassay double antibody techniques. The laboratory diagnosis has been reviewed elsewhere.[23]

Percutaneous transfemoral selective angiography was performed in all patients, utilizing the right femoral artery and the modified Seldinger technique.[12] Catheterizations were done with a No. 7 French polyethylene visceral catheter or No. 5 French Kifa catheters with side holes. The smaller catheters are preferred and used when feasible.

Meglumine iothalamate (Vascoray) or diatrizoate meglumine (Renografin 76 per cent) was used as the contrast medium. A volume of 50 to 60 ml. was injected into the celiac artery, and 40 to 50 ml. was injected into the superior mesenteric artery. We tried to deliver a bolus of contrast medium that would not cause significant reflux into the aorta or recoiling of the catheter. The contrast medium was injected within a period of 5 or 6 seconds. This usually meant

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From the Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

that the injection rate was 8 to 12 ml./s., using a Medrad power injector.

Twenty-three of the 24 patients had selective celiac injections. The other patient had an occlusion of celiac origin proved at surgery. Twelve patients also had the superior mesenteric artery injected. Eight patients had selective injections: 4 splenic, 1 hepatic, and 3 gastroduodenal. The selective techniques were done as indicated, if technically feasible.

Stereoscopic filming technique has been used in all cases since 1971. The filming sequence covers a minimum of 20 seconds. The usual series is 2 exposures per second for 5 seconds, 1 per second for 5 seconds, and 5 delayed films at 2 or 3 second intervals.

Magnification and subtraction techniques were done as needed; however, the negative study (Case 21) was not completed until both techniques were utilized; subtraction techniques are now done routinely.

Continuous monitoring of the blood glucose level was routinely done before, during, and after surgery, and the operation was not terminated until the characteristic elevation of the glucose level after tumor removal was noted.[7] A close consultative relationship existed between the surgeon and the radiologist to ensure accurate correlation of the location of the tumor as seen angiographically and its exact anatomic site of surgical resection. Recently, the surgeon has been requested, when feasible, to mark the bed of the resected tumor with small metallic vascular clips so that the location can be identified on postoperative studies and compared with the site noted on the angiogram.

RESULTS

Twenty-four patients with a clinical diagnosis of hypoglycemia and organic hyperinsulinemia were studied angiographically (Table 1). Of these, 21 patients had at least 1 islet-cell tumor identified angiographically, 17 before operation. Of the 17 patients in whom a small, single benign islet-cell tumor was successfully removed, 16 had the tumor identified angiographically. Of these 16 lesions, 12 were correctly localized before operation and 4 were seen in retrospect. Two of these 4 tumors (Cases 9 and 16) were seen by the use of subtraction technique, which was not done initially, and 1 lesion (Case 10) was not accurately localized, although a suspicious area at the junction of the head and body was identified preoperatively. The fourth lesion (Case 17) was one of our early experiences and, although the quality of the study was poor, the tumor was seen in retrospect but was not appreciated because of its small size. In this instance, a total pancreatectomy was done, and it is of interest to note that the diagnosis was not confirmed pathologically until approximately 1 week later, after complete sectioning of the gland. A characteristic glucose elevation after the staged removal of the pancreas at surgery was observed.

False-Negative Finding. One patient (Case 18) with a negative preoperative angiographic localization had a 1.3 cm. tumor in the uncinate process at surgery. This tumor did not exhibit any roentgenographic findings even in retrospect. The celiac and superior mesenteric arteries were both injected, and magnification and subtraction techniques were utilized; however, selective catheterization could not be accomplished. It is doubtful that this would have helped, as the pancreatic vascularity was well demonstrated by the other injections.

Malignant Tumors. Two tumors in 2 patients, respectively, were suspected before operation to be malignant islet-cell tumors because of their size and vascular characteristics. One patient (Case 7) had a 3.5 cm. tumor at the junction of the body and tail, and this lesion was successfully removed. There was no evidence of metastasis, and he has done well since the removal 3 years ago. The second patient (Case 13) had a large 12 by 7 by 7 cm. islet-cell tumor that caused obstruction of the splenic vein and had metastasized to the local lymph nodes.

Multiple Tumors. Three of the 21 patients with angiographically positive find-

TABLE I

CASES OF INSULIN-PRODUCING ISLET-CELL TUMORS

Case	Sex and Age (yr.)	Quality of Study	Date of of Study	Preoperative Angiogram	Tumor Location	Tumor Size (cm.)	Vascularity	Surgery	Comments
1	F, 55	Good	3/72	Pos.	Head	1.2	Hypovascular	Enucleation	Previous partial pancreatectomy
2	F, 61	Good	9/71	Pos.	Body	1.1	Hypovascular	Enucleation	
3	F, 63	Good	2/72	Pos.	Head	2.0	Hypovascular	Enucleation	
4	F, 36	Fair	6/69	Pos.	Body	1.5	Hypovascular	40 per cent pancreatectomy	
5	M, 45	Fair	2/70	Pos.	—	—	—	60 per cent pancreatectomy	Doing well, feels better
6	F, 52	Good	10/70	Pos.	Body-tail	0.3–1.0	Vascular	60 per cent pancreatectomy	Multiple tumors (7)
7	M, 27	Good	6/71	Pos.	Body-tail	3.5	Vascular	40 per cent pancreatectomy	Malignant tumor
8	F, 21	Good	2/73	Pos.	Head	1.0	Vascular	Enucleation	
9	M, 62	Good	1/73	Neg.	Tail	1.5	Hypovascular	Enucleation	Seen with additional subtraction, not done before
10	F, 64	Fair	8/73	Neg.	Head	1.1	Vascular	Enucleation	Wrong location initially—seen with subtraction
11	F, 23	Good	6/71	Pos.	Body	1.0	Vascular	Enucleation	
12	M, 23	Good	1/73	Pos.	Body-tail	0.4–3.0	Vascular (cystic, 3)	Enucleation and distal pancreatectomy	Multiple tumors (6)
13	M, 55	Good	5/73	Pos.	Body-tail	12 by 7 by 7	Vascular	80 per cent pancreatectomy	Malignant tumor
14	M, 33	Fair	5/72	Pos.	Tail	1.5	No specimen	40 per cent pancreatectomy	
15	F, 28	Good	7/73	Pos.	Body	1.5	Vascular	Enucleation	
16	F, 41	Poor	3/69	Neg.	Body	1.3	Hypovascular	Enucleation	Seen with subtraction—edge of film
17	F, 69	Poor	11/69	Neg.	Body	0.6	Hypovascular	Total pancreatectomy	Missed, too small, not appreciated
18	F, 61	Good	1/72	Neg.	Head	1.3	No specimen	60 per cent pancreatectomy	Cannot be seen—even in retrospect
19	F, 46	Good	1/74	Pos.	Body	0.3–1.8	Hypovascular	60 per cent pancreatectomy	Multiple tumors (7)
20	M, 72	Good	2/74	Pos.	Body	1.1	Vascular	70 per cent pancreatectomy	
21	F, 52	Good	11/72	Neg.	—	—	—	None	Factitious hypoglycemia
22	F, 40	Good	2/74	Pos.	Head	1.5	Hypovascular	60 per cent pancreatectomy and enucleation	
23	F, 47	Good	7/74	Pos.	Head	1.2	Vascular	—	Previous partial pancreatectomy
24	M, 24	Good	6/74	Pos.	Body	2.0	Vascular	Enucleation	

ings had multiple tumors. Multiplicity was indicated in all 3, but not all of the tumors were seen. There were 20 tumors pathologically in these 3 patients, and 12 of these 20 could be identified, 8 before operation. Three of the tumors that were not seen in 1 patient (Case 12) were considered pathologically to be cystic islet-cell tumors of the pancreas, and none of these was visualized. In all 3 patients, a 75 per cent or less distal pancreatectomy removed all of the insulin-producing islet-cell tumors.

Two patients in whom an insulin-producing islet-cell tumor was suspected clinically did not have such lesions: this was confirmed surgically in 1 and roentgenographically in the other. One patient (Case 5) had a false-positive finding on angiography. The patient underwent a distal 60 per cent pancreatectomy in spite of a negative exploration because of the strong suggestive evidence on the angiogram of a tumor in the body of the pancreas. The only positive finding at surgery was an inflammatory lymph node near the body, which could be seen on the angiogram and was mistakenly identified as the lesion. Monitoring of blood glucose levels during surgery did not reveal the characteristic elevation. The patient was improved 1 year after surgery. The possibility exists that the hypoglycemia was related to some cause other than islet-cell tumor.[25]

The second patient (Case 21) was not operated on. Study of the pancreas included selective celiac, hepatogastroduodenal, sple-

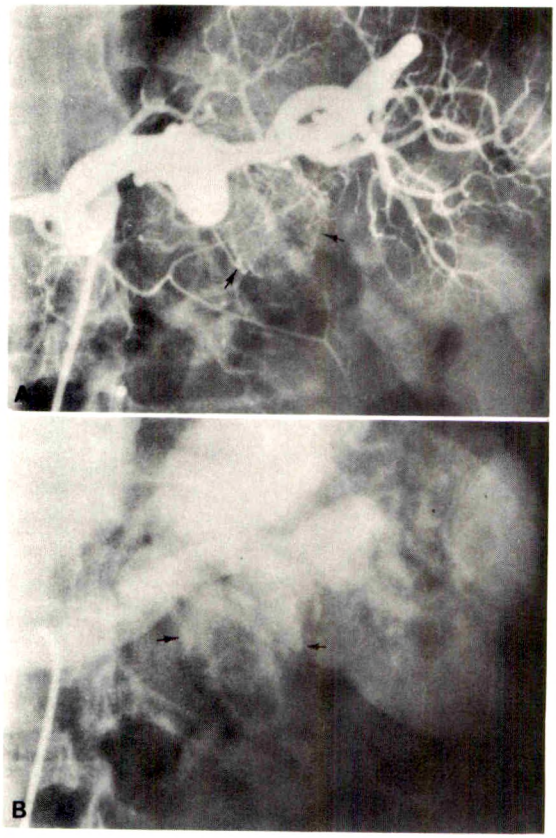

FIG. 1 (*A*) Early arterial phase, 2.5 seconds, shows displaced vessels surrounding large vascular mass. (*B*) Late venous phase, 18 seconds, shows well-demarcated, 4.0 cm. homogeneous mass inferior to splenic vein.

nic, and superior mesenteric injections. Magnification and subtraction techniques were also used, but results were negative. Follow-up evaluation showed continued low levels of blood sugar, but the frequency of her black-outs has decreased since she has been given diphenylhydantoin. She now does not demonstrate Whipple's triad, and her condition has been diagnosed as factitious hypoglycemia.

The characteristic homogeneous vascular blush persisting into and through the venous phase was seen in all patients with positive findings. In the patients with larger tumors, especially the malignant ones, displacement of vessels, tortuosity, and neovascularity could be identified (Fig. 1, *A* and *B*). Usually, the blush could be identified within the first 2 to 4 seconds, and it persisted 12 to 16 seconds.

Occult Tumors. Six occult insulin-producing islet-cell tumors could not be identified or palpated at exploration. Close cooperation and consultation between the surgeon and the radiologist allowed a persistent effort to be made and demonstrated the decisive value of preoperative angiography. A 70 per cent pancreatectomy would have resulted in a cure in only 2 of the 6 patients (Cases 11 and 14). The other 4 lesions were located in the head of the pancreas, which is an extremely difficult area for the surgeon to evaluate because of its location and thickness.

Without preoperative angiographic localization, 2 of the 6 patients (Cases 1 and 23), who had already had 60 per cent pancreatectomies prior to their referral, might have had to undergo total resection in order to locate the tumors. One patient (Case 1) had the tumor located inferiorly and posteriorly to the gastroduodenal artery (Fig. 2, *A–C*). The surgeon could not palpate the tumor and stated in his operative report that he "would not have found the lesion without the help of angiography" (Table II).

One patient (Case 23) had undergone angiography elsewhere, and a tumor in the tail of the pancreas was diagnosed. One month later, she underwent a 60 per cent pancreatectomy, but her symptoms were not relieved. A repeat angiographic examination 5 months later again did not demonstrate a tumor, and she was referred to us for further evaluation. Another angiogram was then performed. The tumor was apparent on our first injection into the celiac artery (Fig. 3, *A–C*). With the aid of the stereoscopic technique, we were able to direct the surgeon to the anterior location of the tumor in the head of the pancreas. Because the tumor could not be palpated or located, an incision was made in the indicated area and the tumor was found.

One patient (Case 3) had angiographic evidence of complete occlusion of the celiac and inferior mesenteric arteries (Fig. 4, *A–C*). The sole input of blood to the gastro-

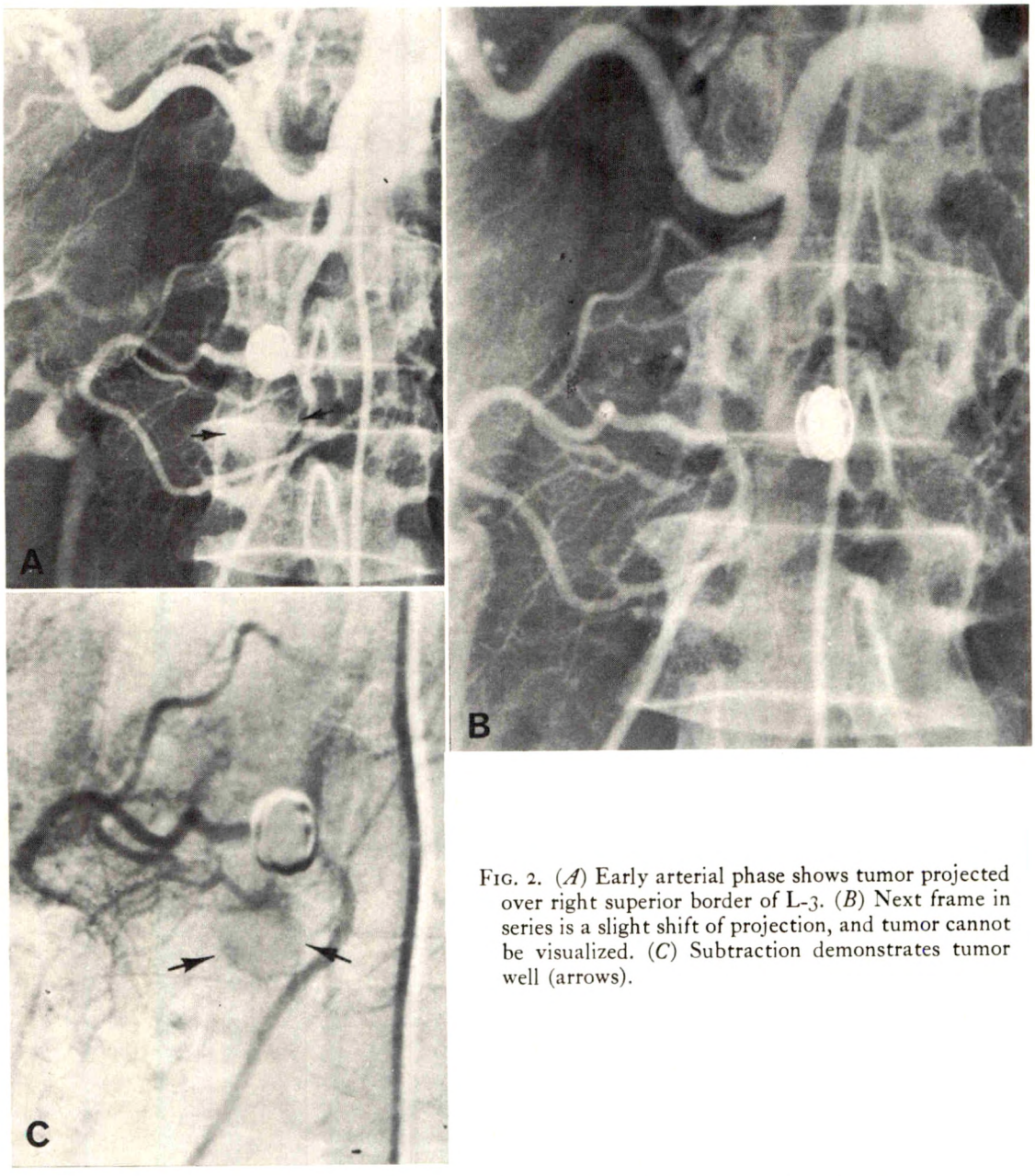

Fig. 2. (*A*) Early arterial phase shows tumor projected over right superior border of L-3. (*B*) Next frame in series is a slight shift of projection, and tumor cannot be visualized. (*C*) Subtraction demonstrates tumor well (arrows).

intestinal tract was the superior mesenteric artery and through the gastroduodenal artery. The tumor was located beneath the gastroduodenal artery, which had to be preserved as an essential vessel.

One patient (Case 10) had positive preoperative angiography, but the location of the tumor found at surgery did not correspond to that indicated on the angiogram. The surgeon was unable to locate the tumor in the body of the pancreas at the site indicated. A review of the roentgenograms suggested a possible second site in the head. The tumor was then located. A subsequent subtraction film confirmed the location in the head, but this was not done originally.

Vascularity. Pathologic specimens were available for review in 15 patients who had single, benign insulin-producing tumors. There was no relationship between the de-

TABLE II

COMMENTS BY SURGEON ON OPERATIVE REPORT OF OCCULT TUMORS

Case	Tumor Size (cm.)	Angiographic Location	Comment
1	1.2	Head	"Would not have found the lesion without the help of angiogram" (prior subtotal resection)
3	2.0	Head	"Looked and palpated head, negative; explored tail, negative; back to area on angiogram"
10	1.1	Head	"Considerable difficulty finding tumor"
11	1.0	Body	"Negative exploration; finally went to area shown on angiogram and found tumor"
14	1.5	Tail	"Could not find anything at surgery; finally did blind distal pancreatectomy, found tumor"
23	1.2	Head	"Unable to palpate tumor; opened anterior head of pancreas as seen on angiogram and found tumor" (prior subtotal pancreatectomy)

gree of vascularity of the tumor and the size or location of the tumor at surgery. Histologically, 8 of the tumors (sizes 0.6 to 2.0 cm.) were considered to be hypovascular and 7 (sizes 1.0 to 1.5 cm.) were considered to be vascular. All 15 could be identified by angiography.

There were no special locations where degree of vascularity seemed to influence visualization. Special reticulin stains were not done for purposes of this review.

Operative Times. Preoperative localization has reduced the operative times, thereby possibly reducing patient morbidity. Several cases should be examined more closely. One patient (Case 5) had a false-positive angiogram, which prolonged exploration of the pancreas and necessitated distal pancreatectomy. One patient (Case 14) had a positive angiogram and yet the surgeon could not locate the tumor, thus requiring a distal pancreatectomy. Another patient (Case 18), who had a negative angiogram, underwent a 70 per cent pancreatectomy before the tumor was finally located in the uncinate process. One patient (Case 17), who had a negative preoperative angiogram, had a radical total pancreatectomy before a classic response to intraoperative glucose monitoring was noted. All of these patients required longer operative times than that required when a lesion could be seen on preoperative angiograms or easily located at surgery.

DISCUSSION

After reviewing all cases in the literature, including their 6, Bookstein and Oberman[4] in 1966 reported that an accuracy of 20 per cent in the angiographic localization of islet-cell tumors of the pancreas probably was about the best that could be expected. A later report from the same institution suggested an over-all accuracy rate of 38 per cent in localizing insulin-producing islet-cell tumors.[22] Other higher success rates most often refer only to cases when there is a single lesion.[1,3,6,10,15] Kavlie and White,[11,24] however, suggested that angiography is not indicated, as they failed to localize the tumors in any of the 10 patients studied. The incidence of angiographic complications was significant.

Our own experience, in which tumors were demonstrated angiographically in 21 of 24 patients and also in 1 additional patient (not counted) in whom no insulin-producing tumor was noted, gives an over-all case accuracy of 91 per cent. There were no complications of the angiographic examination.

Our experience and that found in the

literature convince us that angiography should not be an elective procedure but should be a mandatory examination once the clinical diagnosis has been established.

Much has been written and alluded to regarding the ability to visualize these tumors, dependent on their vascularity.[1,4,22] We, like Fujii *et al.*,[9] did not find a significant correlation among size, location, and degree of vascularity of the tumors. We did find that important aspects in the ability to visualize these tumors are the proper roentgenographic and technical considerations. Madsen and Hansen[15] suggested that utilization of 88 to 90 kvp. tends to result in low differences in contrast and that by lowering the kvp. to the 70 to 75 range and increasing the milliamperage, a better technical examination will result.

One of our cases (Case 23) is a good example in support of this recommendation. This patient had a good technical examination at another institution. A repeat angiographic examination 5 months later did not demonstrate the tumor. The tumor was apparent on our first injection in the celiac artery. However, even in retrospect, we could not identify the tumor on either of the 2 previous angiograms. The only difference appeared to be the technical factors involved. The first film was of very low contrast, and the second film was slightly underexposed. Differences in contrast between structures during the parenchymatous phase are necessary if subtle differences are to be appreciated. Attention to technical detail is paramount to accurate diagnosis. We suggest that in correct preoperative localization, the technical expertise of the investigator may be more important than the size, location, or vascularity of the insulin-producing islet-cell tumor.

Laroche *et al.*[14] stated that blind resection of the body and tail of the pancreas is only successful in about 50 per cent of patients when the insulinoma cannot be found. Mengoli and Le Quesne[17] reviewed the results of blind pancreatic resection in 47 cases reported since 1958. They found 11

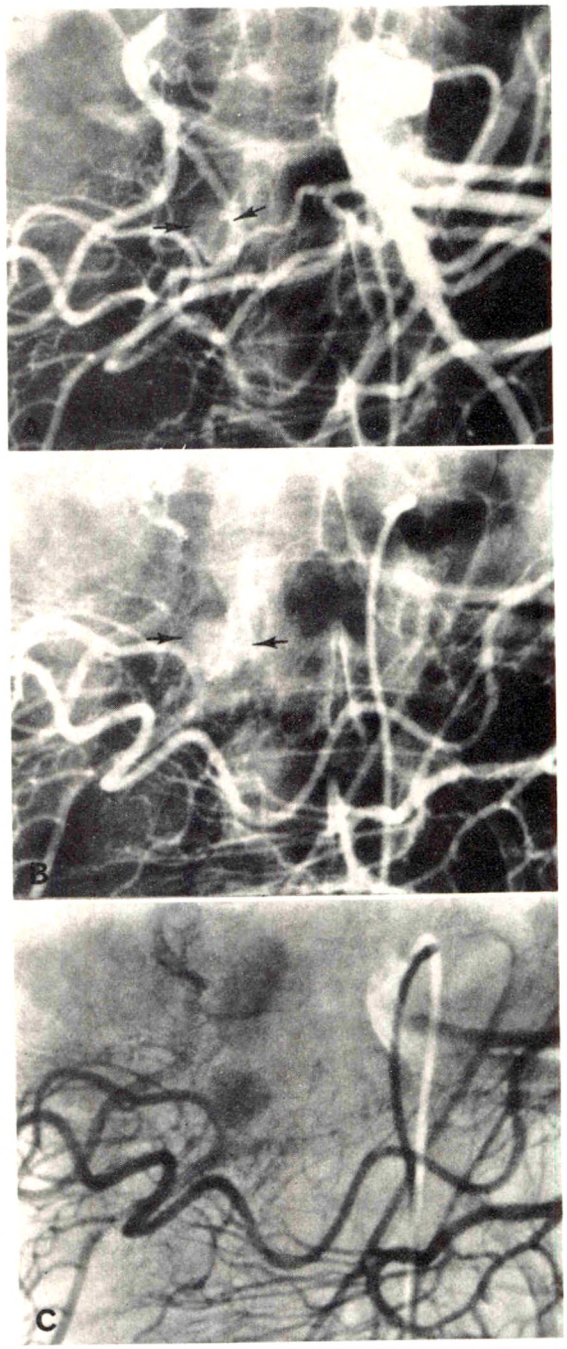

Fig. 3. (*A*) Four seconds after beginning injection, a faint blush is projected between pancreaticoduodenal arcades. (*B*) Four seconds later, 1.2 cm. classic blush now fairly well seen. (*C*) Subtraction of *B* confirms dense homogeneous stain.

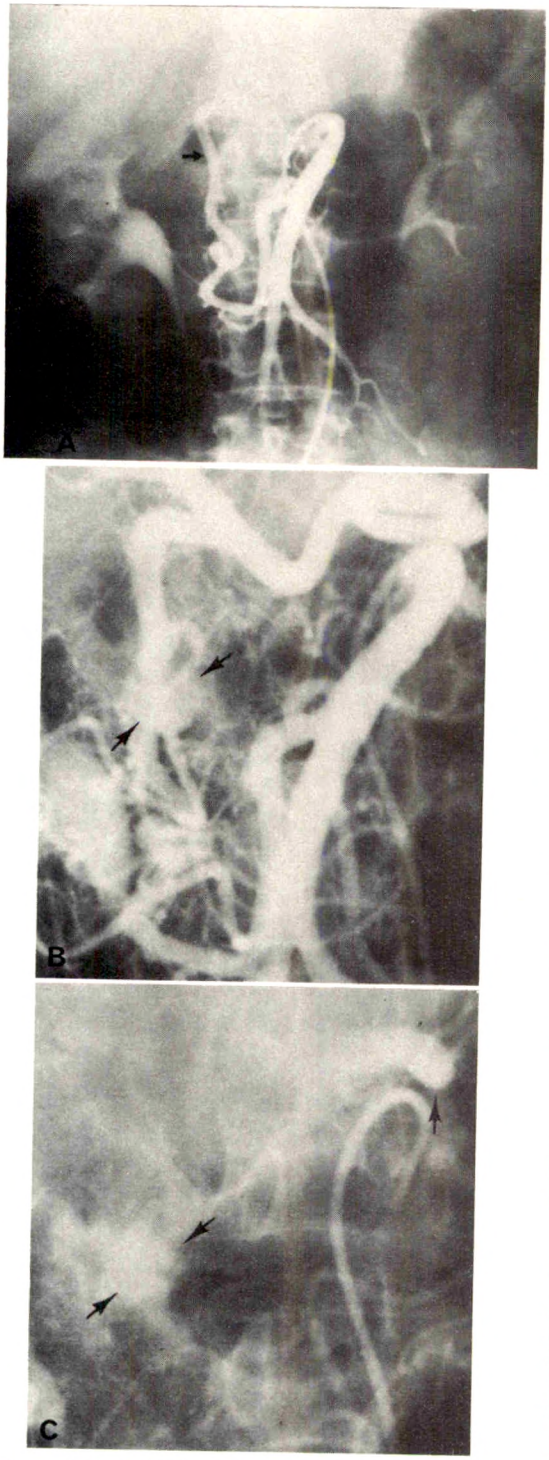

FIG. 4. (*A*) Superior mesenteric artery injection; retrograde filling of gastroduodenal to celiac artery. (*B*) Homogeneous blush beneath gastroduodenal artery. (*C*) Venous phase, classic blush. Single arrow shows celiac origin occluded.

cases of occult tumors, 21 in which the tumor was found at a second operation, 3 in which the tumor was found at autopsy, and 12 in which the tumor was never found. These results were somewhat better than those noted prior to 1958; Moss and Rhoads[19] reported that in 99 of 165 blind resections, a tumor was never found (60 per cent). Thirty-six patients had occult tumors, and 30 had the lesion discovered at a second operation.

The major problem, as elucidated by Filipi and Higgins[8] and Wolfe *et al.*,[26] is the occult tumor that cannot be palpated at surgery. Although only 3 such cases have been reported[1,6] in which the occult tumor was angiographically localized before operation, we found that 6 of 12 patients (50 per cent) with such tumors were located surgically only because of the preoperative angiographic localization (Table II). At least 1 other patient (Case 17), who eventually underwent total pancreatectomy, might have had a lesser surgical procedure if the tumor had been diagnosed preoperatively.

The *sine qua non* of all good vascular roentgenologic techniques is the demonstration of the complete blood supply to the area in question. Whether to inject the celiac and superior mesenteric arteries simultaneously or sequentially, or in one and not the other vessel, is an individual preference and judgment. Although we utilize selective techniques when needed and technically feasible, perhaps Boijsen and Samuelsson[3] and Deutsch *et al.*[5] are correct in suggesting that selective injections may result in erroneous diagnosis.

One of our cases (Case 22) demonstrated the value of stereoscopic serial filming (Fig. 5, *A* and *B*). This technique is used on all series unless magnification is employed, and it has become a most valuable adjunct. The anteroposterior study shows the characteristic vascular blush overlying the inferior midportion of L-1, and the next frame shows that it projected over the right side of the first vertebral body. This area is easily seen. Stereoscopy has established or confirmed the diagnosis and location of the

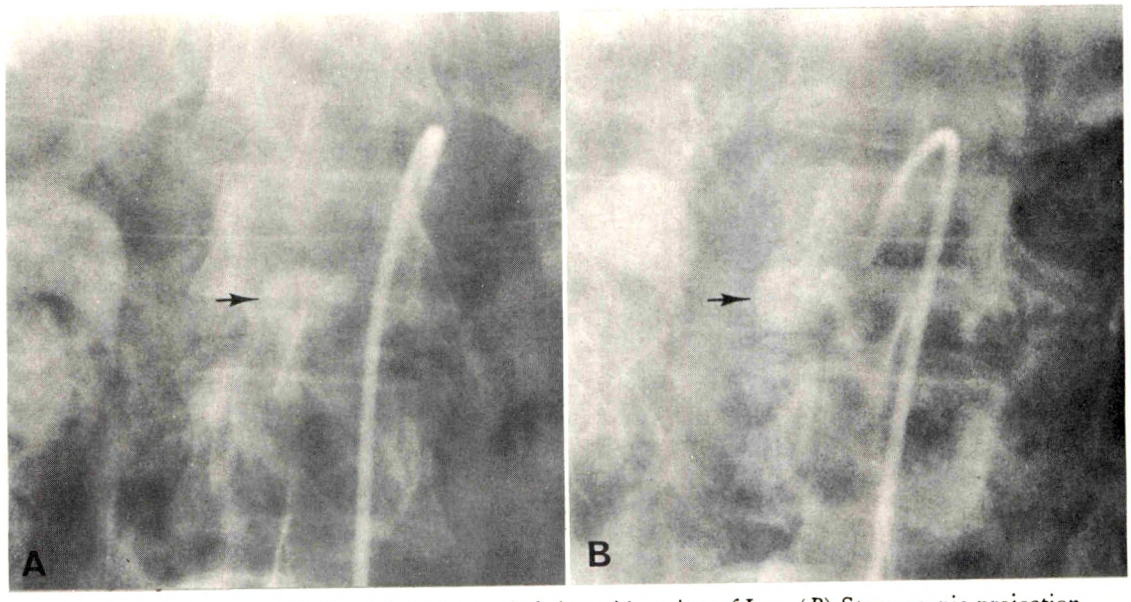

Fig. 5. (*A*) A 1.5 cm. blush projected over inferior midportion of L-1. (*B*) Stereoscopic projection demonstrates tumor projected over right side of L-1.

tumor within the substance of the pancreas in 12 of our patients. One case (Case 15) demonstrated a very vascular islet-cell tumor that might have been mistaken for the left adrenal gland (Fig. 6, *A–C*). Stereoscopy removed this confusion because it afforded visualization of the tumor in the superior margin of the pancreas, where it was easily enucleated at surgery.

Magnification has not yet allowed us to make a diagnosis that was not already suspected, but it has aided in confirming our findings in 4 patients. In 2 patients (Cases 16 and 17) who had negative preoperative arteriograms, good quality magnification and stereoscopy were not done but may have helped.

Röbins *et al.*[22] did routine subtraction in all of their cases but they also failed to establish a diagnosis that was not already suspected. In 1 of our patients (Case 24), the diagnosis would not have been made without the aid of the subtraction technique (Fig. 7, *A* and *B*). The study of the late venous phase showed at least 2 questionable areas, one over the spine and another in the head. The subtraction film of the same frame clearly demonstrated a bilobed 2 cm. tumor located in the body of the pancreas. The location and appearance of the tumor correlated exactly to those shown on preoperative angiography—a fact commented on by the surgeon. Since becoming part of our routine, the subtraction technique has allowed us to eliminate many confusing shadows that could be mistaken for tumors and to confirm our initial localization in 5 other cases.

The causes for false-positive and false-negative diagnoses have been enumerated in other papers.[1,5,13,16] Our 1 case with a false-positive finding involved an inflammatory lymph node, mistakenly considered to be an islet-cell tumor. Inflamed lymph nodes have been found at surgery in 2 other cases, but these were not visualized on angiography, even in retrospect. Hypervascularity of the gland, as described by Reuter,[21] and inflammatory lymph nodes probably are the most frequent causes for a false-positive diagnosis. Other pancreatic lesions also can give a positive appearance within the pancreas.[10]

SUMMARY

The significant morbidity and mortality associated with pancreatic surgery for islet-cell tumors indicate the need for accurate,

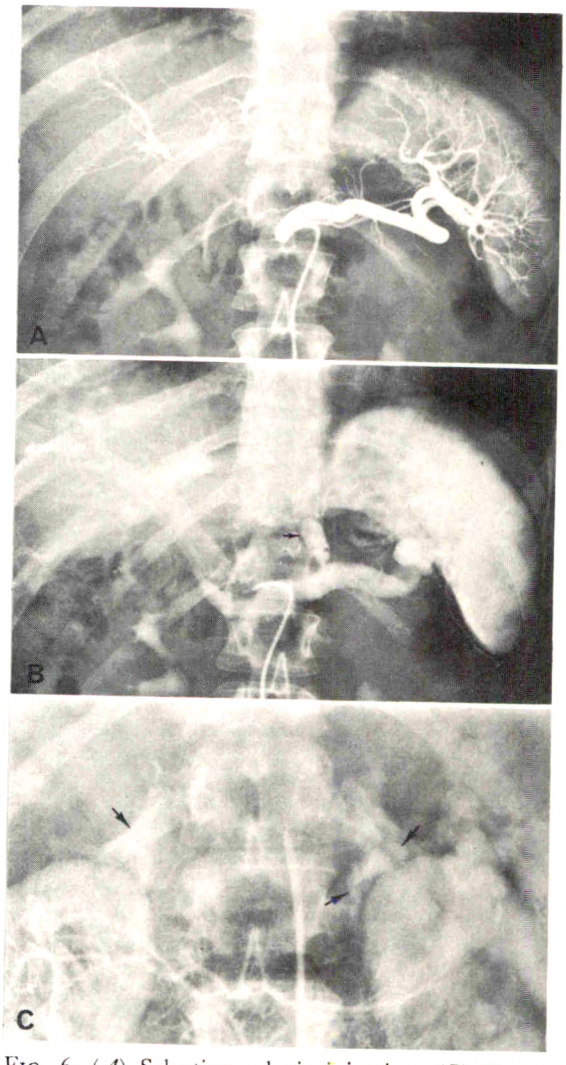

FIG. 6. (*A*) Selective splenic injection. (*B*) Dense homogeneous blush projected above splenic vein (arrow). (*C*) Venous phase of midstream aortogram shows adrenal glands (arrows).

reliable identification and preoperative localization of insulin-producing islet-cell tumors. The results of this study indicate that angiographic examination of the pancreas can detect such tumors with a degree of accuracy greater than 90 per cent, if attention is paid to the technical quality of the examination. This attention is as important for the accurate diagnosis as are the size, location, and vascularity of the tumor. Vascularity of the tumor as assessed histologically may not have as important a role in the diagnosis as previously suggested.

Supplementary techniques such as stereoscopy, subtraction, magnification, and selective injections are also important. We were able to demonstrate 6 of 12 occult insulin-producing islet-cell tumors within the pancreas preoperatively by means of such techniques, which otherwise might have resulted in a partial pancreatectomy without identification of the tumor by the surgeon. The small tumor, less than 5 mm. in diameter, will remain extremely difficult to localize, but attention to technique and utilization of the suggested roentgenologic methods will help in localization.

In all cases of clinically proved insulin-producing islet-cell tumors of the pancreas, an attempt should be made to localize the lesion preoperatively by angiography. Successful localization provides confirmation

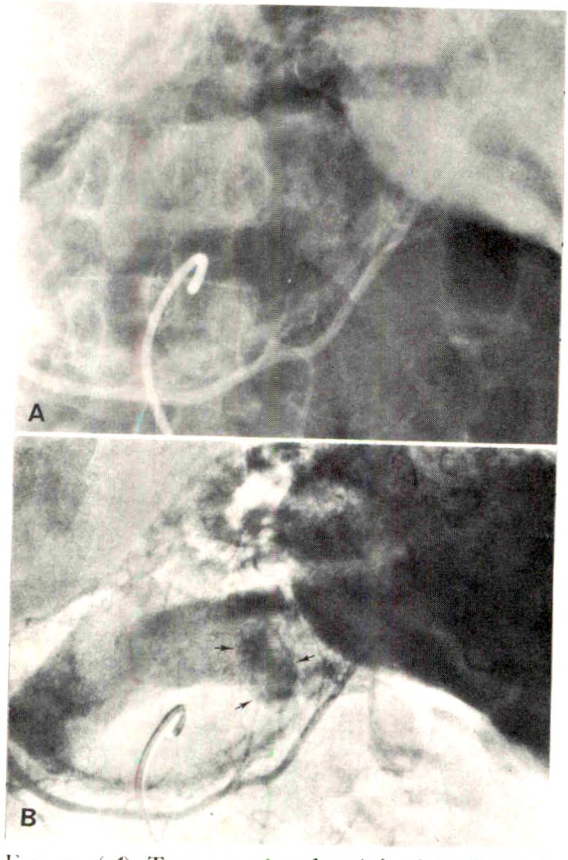

FIG. 7. (*A*) Ten seconds after injection. Several suggestive areas of tumor localization. (*B*) Subtraction of *A* demonstrates a 2.0 cm., bilobed, well-demarcated islet-cell tumor.

to the internist and enhances the surgeon's chances for deciding upon the most appropriate surgical procedure, thereby reducing the risk to the patient of subsequent morbidity.

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STENOSING LESIONS OF THE BILIARY TREE*

EVALUATION WITH ENDOSCOPIC RETROGRADE CHOLANGIOGRAPHY (ERC) AND PERCUTANEOUS TRANSHEPATIC CHOLANGIOGRAPHY (PTC)

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NUMEROUS roentgenologic methods of investigation have been employed in an attempt to distinguish between the intrahepatic and extrahepatic causes of jaundice.[2] Intravenous cholangiography and percutaneous transhepatic cholangiography have both contributed to an increased yield of preoperative diagnosis. In the last few years the advent of the flexible fiberoptic duodenoscope and the successful cannulation of the pancreatic duct and biliary tree have provided an even greater opportunity for the clinician to make a preoperative diagnosis of the cause of jaundice.[4,6,7,10–12,16,19] The endoscopic retrograde cholangiogram (ERC) is the result of a cooperative effort between the endoscopist and the radiologist.[17] While complications have occurred with this technique,[3,5] they are usually minor and the technique is far less invasive than percutaneous transhepatic cholangiography (PTC), which, with even the most modern techniques, has a complication rate of 10 to 12 per cent.[9,14]

Hepatocellular disease and biliary stone disease account for most cases of jaundice or intermittent signs and symptoms related to the biliary tree. Included in the less frequent causes of jaundice are the stenosing or stricturing lesions of the biliary tract. The purpose of this report is to present our experience with 10 cases in which the prominent roentgenographic features of localized or diffuse stenotic lesions of the biliary tree were demonstrated by ERC and/or PTC.

From January, 1972 to July, 1974, 87 patients were studied with endoscopic retrograde pancreatocholangiography at the Mallinckrodt Institute of Radiology. Nine of these patients were shown to have localized or diffuse stenosing lesions of the biliary tree. Eight of these 9 patients were studied with ERC alone, while one patient required both ERC and PTC for diagnosis. During the same period of time a tenth patient with a by-passing choledochojejunostomy, who thus could not be studied with the endoscopic technique, was evaluated for intermittent jaundice and fever with PTC.

MATERIAL AND METHOD

All patients were examined with the Olympus duodenofiberscope JF Type B. Premedications consisted of atropine 0.6 mg. and meperidine 50 mg. intramuscularly, diazepam intravenously (usual dose 10–20 mg.) and a pharyngeal spray containing 2 per cent tetracaine. Occasionally, additional diazepam was needed during the procedure. Intravenous atropine, 0.2 mg. or glucagon, 1 mg. is used when needed to produce hypotonia of the duodenum. The positioning of the patient and techniques used to locate and intubate the duodenal papilla are as described by Vennes and Silvis.[20]

PTC is performed in this department with an 18 or 20 gauge teflon sheathed needle, 6 or 8 inches in length, using a right mid-axillary approach under fluoroscopic control. Sodium iothalamate 66.8 per cent (Conray 400) diluted with an equal volume of normal saline is the contrast agent used in both ERC and PTC. Volumes of the contrast solution ranging from 15 to 75 cc. may be required depending on the

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TABLE I

SUMMARY OF CASES

Case No.	Patient Age (yr.)	History	Other Roentgenographic Studies	ERC and PTC Findings	Operative Findings and Pathologic Diagnosis
I	J.F. 28 M	11 yr. ago—liver failure of unknown etiology 5 yr. ago—onset of ulcerative colitis Recent history of intermittent jaundice	BE—changes of chronic ulcerative colitis	ERC: stenosis of common bile duct and intrahepatic ducts consistent with sclerosing cholangitis	Liver bx (needle): pericholangitis with fibrosis around ducts
II	E.L. 55 F	20 yr. history of ulcerative colitis Intermittent jaundice—1 yr.	IVC: nonvisualization	ERC: narrowing of common bile duct and intrahepatic ducts consistent with sclerosing cholangitis	Liver bx (needle): fibrosis in periportal spaces suggestive of large duct obstruction
III	H.W. 38 M	7 yr. ago—jaundice; sclerosing cholangitis diagnosed at another hospital Since then, persistent jaundice and liver failure		ERC: stenosis of common bile duct and intrahepatic ducts, consistent with sclerosing cholangitis	Liver bx (needle): cholestasis, portal fibrosis and inflammation Previous liver bx: reported consistent with sclerosing cholangitis
IV	J.N. 18 M	6 mo. history of abdominal pain, considered secondary to pancreatitis; however, elevated alkaline phosphatase values were found	Normal BE and UGI examination	ERC: normal common bile duct; areas of narrowing of intrahepatic ducts. Variation of sclerosing cholangitis considered	Liver bx (needle): sclerosing reaction (fibrosis) in intralobular portal tracts with duct proliferation and pericholangitis—consistent with sclerosing cholangitis
V	J.H. 75 M	6 mo. prior to admission developed sudden onset of jaundice; cholecystectomy performed. T-tube cholangiogram interpreted as a stricture of common bile duct. Since then persistent jaundice		ERC: 0.5 cm. stricture at junction of intrahepatic ducts with some tapering of common bile duct. Intrahepatic ducts not well visualized	Operation: benign fibrous stricture of common bile duct; multiple liver abscesses noted. Choledochojejunostomy performed. Open liver bx: Ascending cholangitis and pericholangitis with narrowing of intrahepatic ducts. Operative and postop. T-tube cholangiogram: multiple intrahepatic strictures—? secondary sclerosing cholangitis
VI	A.J. 60 M	3 mo. history of jaundice; exploratory laparotomy 3 wk. prior to admission. No obvious extrahepatic cause for jaundice found; common bile duct could not be isolated and no cholangiogram performed	Nonvisualizing oral cholecystogram	ERC: stricture at junction of right and left hepatic ducts extending 1 cm. down common hepatic duct; impression—scirrhous cholangiocarcinoma	Undifferentiated scirrhous carcinoma involving junction of hepatic ducts, hepatic artery, and portal vein Partial left hepatic lobectomy and hepatodochojejunostomy performed
VII	G.W. 68 F	Complicated cholecystectomy 3 yr. ago with subphrenic abscess; since then intermittent jaundice	IVC: nonvisualization UGI: normal	ERC: 3 mm. stricture of common bile duct with proximal dilatation	Operation: benign fibrous stricture of common bile duct; choledochoduodenostomy performed
VIII	D.C. 32 F	Cholecystectomy 3 yr. ago complicated with subphrenic abscess and posteriorly draining biliary fistula. 3 mo. history of progressive jaundice		ERC: tapering and narrowing of common bile duct with no visualization above the area of stricture PTC: 1 cm. stricture of common bile duct with proximal dilatation	Operation: benign fibrous stricture of common bile duct; choledochojejunostomy performed
IX	D.M. 35 M	Previous cholecystectomy and choledochotomy; jaundice after removal of T-tube	Original T-tube cholangiogram reported normal	ERC: 3 mm. stricture at level of choledochotomy with proximal dilatation	Operation: benign fibrous stricture at level of choledochotomy—common bile duct repaired
X	A.C. 58 F	13 yr. ago cholecystectomy with postop. complications; 3 mo. after first operation choledochojejunostomy. Since then intermittent jaundice	IVC: air in biliary tree—otherwise poor visualization	ERC: unable to visualize common bile duct; normal pancreatic duct PTC: stricture at choledochojejunal anastomosis—rectangular defect in left hepatic duct resembling foreign body—? retained portion of T-tube	Operation: benign stricture of choledochojejunal anastomosis revised; retained segment of T-tube identified and removed

ERC = Endoscopic Retrograde Cholangiography; PTC = Percutaneous Transhepatic Cholangiography; BE = Barium Enema; IVC = Intravenous Cholangiogram; UGI = Upper Gastrointestinal; bx = Biopsy.

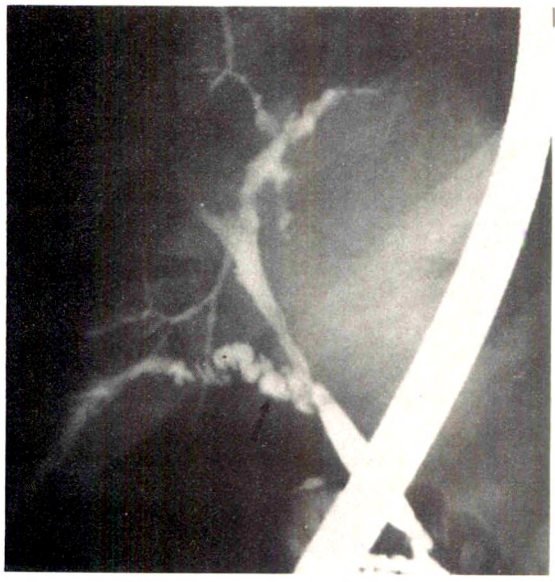

FIG. 1. Case I. Endoscopic Retrograde Cholangiogram (ERC). The study demonstrates narrowing of the common hepatic duct and intrahepatic biliary ducts. The cystic duct is well visualized (arrow). The findings are consistent with primary sclerosing cholangitis.

degree of dilatation on the intrahepatic biliary tree.

FINDINGS

Table I summarizes the history, roentgenographic and pathologic findings of the 10 patients.

Three patients exhibited the intrahepatic and extrahepatic narrowing and marked luminal irregularity consistent with sclerosing cholangitis (Fig. 1; 2, *A* and *B*; and 3). Cases I and II, primary sclerosing cholangitis, were associated with ulcerative colitis. Case III, unassociated with any other disease, had been diagnosed several years before the ERC as primary sclerosing cholangitis at another hospital. The ERC was performed in an attempt to demonstrate a surgically correctable lesion for relief of jaundice.

In Case IV (Fig. 4), strictured areas were seen in only intrahepatic ducts, while the common bile duct appeared normal. The question of an unusual case of sclerosing cholangitis was raised.[13,15] The pathologic specimen demonstrated acute and chronic pericholangitis with fibrosis. Case V (Fig. 5) was initially thought to represent an isolated postsurgical stricture of the common hepatic duct by ERC. Subsequently the operative T-tube cholangiogram demonstrated extensive intermittent narrowing of the intrahepatic duct system, highly sug-

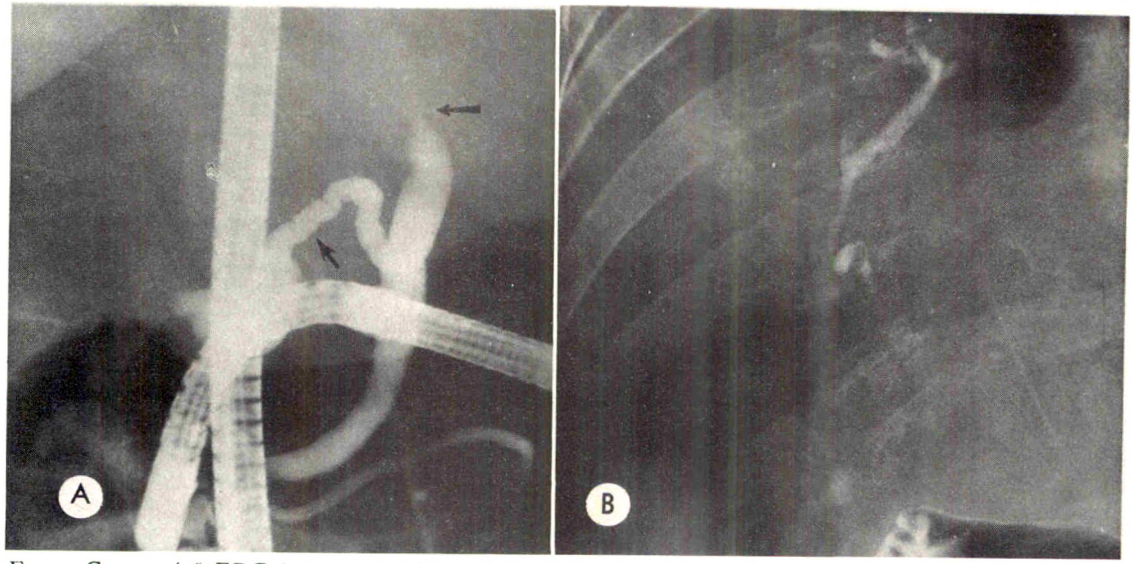

FIG. 2. Case II. (*A*) ERC demonstrates normal distal common duct. The common hepatic duct (long arrow) is tapered, leading to an area of stenosis. The cystic duct is well visualized (short arrow). (*B*) Limited opacification of intrahepatic ducts due to stenosis of common hepatic duct. Irregular areas of narrowing can be seen. The findings are consistent with sclerosing cholangitis.

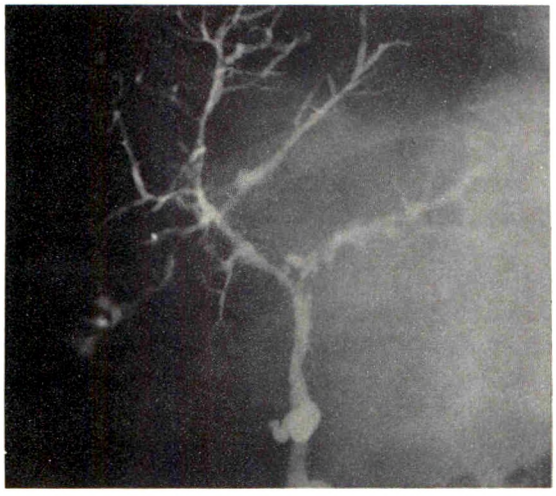

Fig. 3. Case III. ERC. Widespread irregular narrowing of intra- and extrahepatic ducts. "Pruning" of many branches. Appearance of biliary tree consistent with primary sclerosing cholangitis.

Fig. 4. Case IV. ERC. The extrahepatic biliary tree appears normal. There are multiple areas of irregular narrowing of intrahepatic ducts. The cystic duct is well visualized (arrow). Abnormalities involving only the intrahepatic ducts suggest a variant of sclerosing cholangitis.

gestive of secondary sclerosing cholangitis. Open wedge liver biopsy demonstrated marked ascending cholangitis with periductal fibrosis.

The cause of jaundice in Case VI was not determined at the time of the first explora-

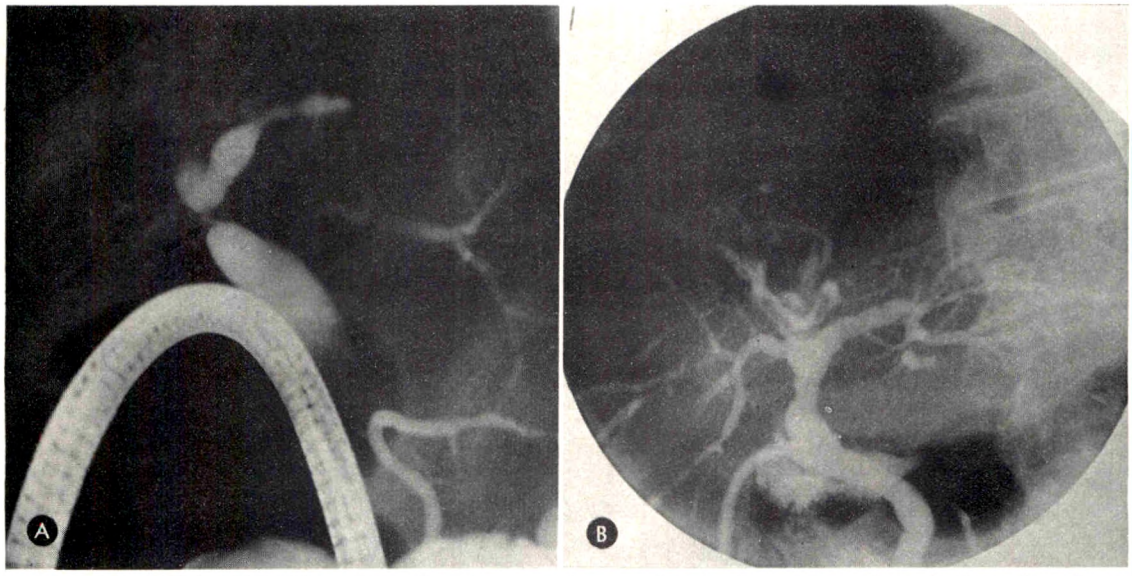

Fig. 5. Case V. (*A*) ERC. There is a discrete area of narrowing in the common hepatic duct thought to represent a benign postoperative stricture (arrow). The slight irregularity of the visualized intrahepatic ducts was not initially appreciated. (*B*) T-tube cholangiogram after repair of fibrous stricture in the common hepatic duct. Multiple areas of irregular narrowing in the intrahepatic biliary tree are seen. Complete picture consistent with secondary sclerosing cholangitis.

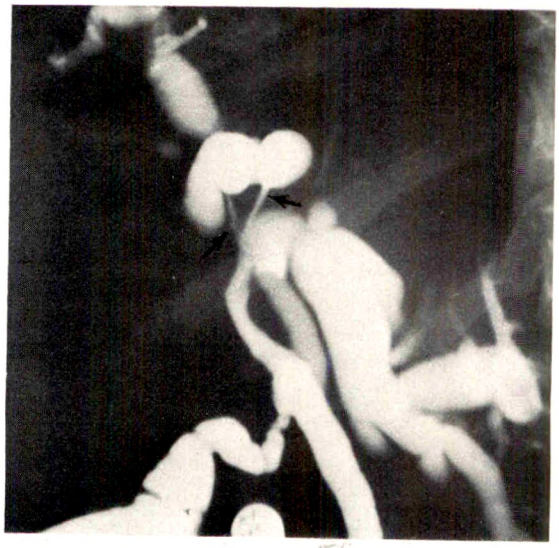

FIG. 6. Case VI. ERC. A stricturing lesion nearly occludes the right and left hepatic ducts close to their junction (arrows) and narrows the common hepatic duct to a less degree. Marked dilatation of the proximal, intrahepatic biliary tree is evident. The gallbladder is well visualized and appears normal. The findings are consistent with a neoplasm, most likely a scirrhous cholangiocarcinoma.

tory laparotomy. An operative cholangiogram had not been performed. The characteristic findings of high-grade stenosis confined to the junction of the left and right hepatic ducts and extending 1 cm. into the common hepatic duct limited the diagnostic possibilities to a neoplasm with a primary scirrhous carcinoma being the most likely cause (Fig. 6). This interpretation was proven at surgery at which time palliative by-passing hepatodochojejunostomy and partial left hepatic lobectomy were performed.

Uncomplicated, discrete, postsurgical extrahepatic strictures were demonstrated in Cases VII, VIII and IX (Fig. 7; 8, *A* and *B*; and 9). The ERC in Case VIII failed to demonstrate the length of stricture or appearance of the biliary tree proximal to the stricture. In this case PTC supplemented the diagnostic evaluation as demonstrated in Figure 8*B*.

In Case X the common bile duct was no longer in continuity with the duodenum. A choledochojejunostomy had been created 13 years earlier. As part of the evaluation of the patient's intermittent jaundice and associated abdominal pain, an endoscopic retrograde pancreatogram was performed which was normal. PTC demonstrated stricture at the choledochojejunal anastomosis and a peculiar rectangular filling defect within an hepatic duct proximal to the stricture. The suspicion of a retained portion of surgical stint was confirmed at operation at which time the anastomosis was revised (Fig. 10).

DISCUSSION

Sclerosing cholangitis is a rare disorder of uncertain etiology characterized by widespread fibrous thickening of the extrahepatic biliary tree with variable involvement of the intrahepatic biliary tree. It is subdivided into a primary and secondary form.[1,18,22] If there has been previous upper abdominal surgery, or specifically biliary tract surgery, the sclerosing cholangitis is considered secondary. The primary form, developing spontaneously, occurs alone or associated with other diseases including ul-

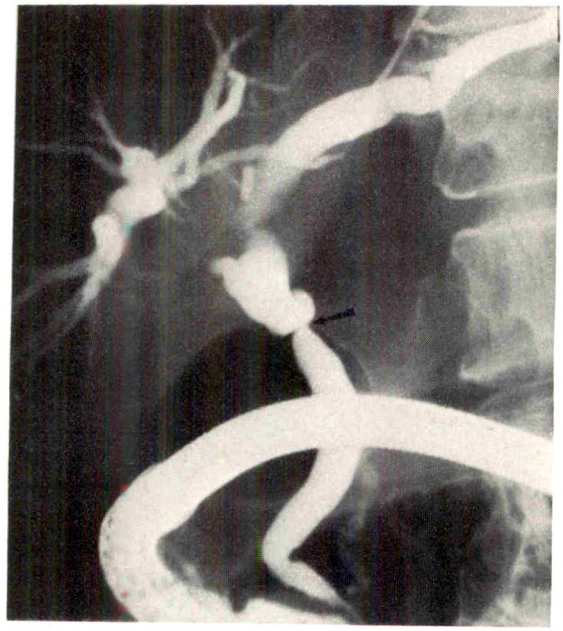

FIG. 7. Case VII. ERC demonstrates a short stricture in the common bile duct at the site of a previous T-tube insertion (arrow). This was proven to be a benign fibrous stricture.

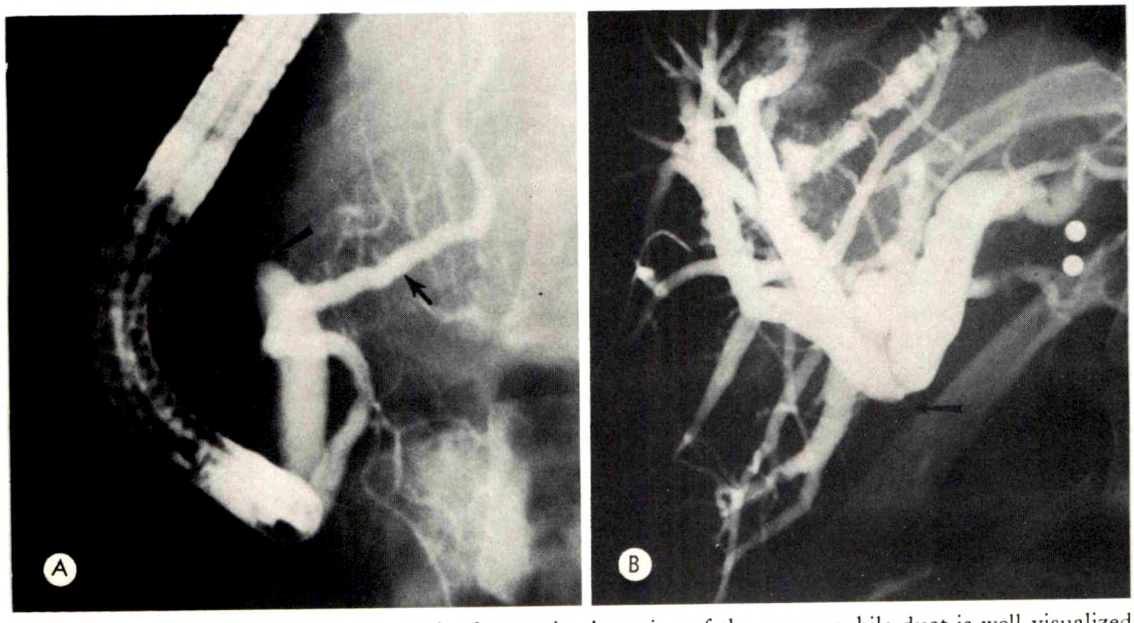

Fig. 8. Case VIII. (*A*) ERC. A stricture in the proximal portion of the common bile duct is well visualized (long arrow). Contrast medium fails to pass into the common hepatic duct or higher. Length of stricture cannot be determined. The pancreatic duct (short arrow) is opacified. (*B*) PTC. Marked narrowing of the common hepatic duct at its origin is present (arrow). The intrahepatic biliary tree is greatly dilated. The PTC clarifies the length of the stricture, supplementing the findings on ERC. This stricture was proved to be a benign, postsurgical fibrous stricture.

cerative colitis, regional enterocolitis, Riedel's struma, retroperitoneal fibrosis, mediastinal fibrosis and retro-orbital tumors. This entity is rarely diagnosed preoperatively. The combination of T-tube cholangiogram results and biopsy findings is utilized in arriving at a definitive diagnosis. At times there is considerable difficulty distinguishing histologically between adenocarcinoma of the bile ducts and sclerosing cholangitis, especially when the periductal glands are distorted by fibrosis and inflammation. The relatively large number of cases of primary and secondary sclerosing cholangitis evaluated here in a 2 year period suggests that endoscopic retrograde cholangiography will not only reveal the presence of this disease more often but will clarify the spectrum of involvement that can be seen in this entity.

Benign strictures of the biliary tree are secondary to surgical trauma in approximately 95 per cent of the cases.[8,21] While some are secondary to surgical accidents, a

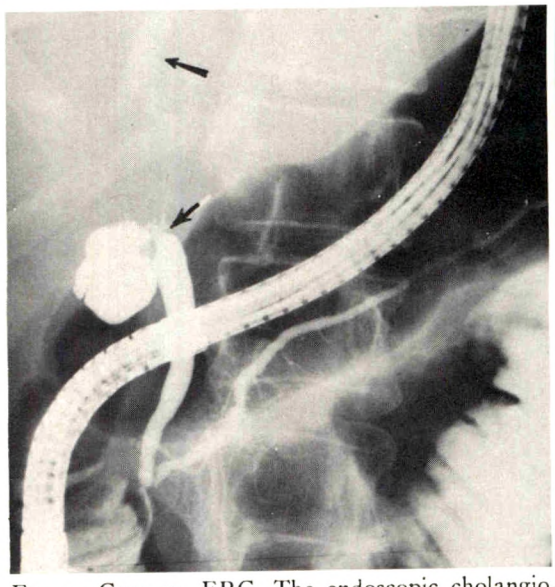

Fig. 9. Case IX. ERC. The endoscopic cholangiogram localizes a pin hole stricture (short arrow) of the common bile duct at the site of a prior choledochotomy. A walled-off postsurgical cavity is seen lateral to the stricture, and a jet of contrast medium, traversing the stricture, faintly opacifies dilated portions of the proximal biliary tree (long arrow). Benign postsurgical stricture.

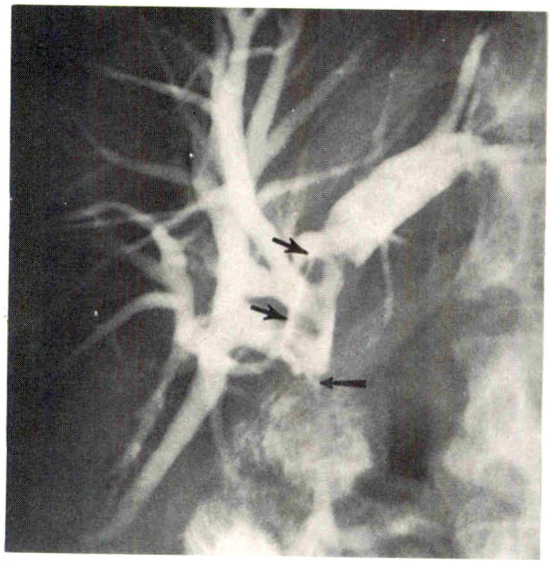

FIG. 10. Case x. PTC. A high-grade stricture at the choledochojejunal anastomosis is demonstrated (long arrow). An ill-defined rectangular filling defect (short arrows) in the dilated left hepatic duct suggests a portion of a retained surgical stint, subsequently proven.

few will appear in patients who have had a routine, uneventful operative procedure such as cholecystectomy with or without common duct exploration. The presence of this stricture is usually not evident in the operative and postoperative T-tube cholangiogram. By the time the patient becomes symptomatic, either ERC or PTC is necessary to establish the diagnosis, as was the situation in Cases VII, VIII, and IX.

In some cases the failure to perform operative cholangiography when confronted with a normal or collapsed appearing extrahepatic biliary tree, results in the failure to diagnose a stenosing lesion of the intrahepatic duct system.[23] Such was the situation in Case VI. While primary tumors of the distal common bile duct will be frequently evident on an intravenous cholangiogram or indirectly suggested by the changes seen on upper gastrointestinal examination, the tumors of the proximal biliary tree frequently remain undetected. It is evident from this Case that endoscopic retrograde cholangiography can be extremely useful in clarifying the nature and extent of such a lesion.

When oral cholecystography and intravenous cholangiography fail to clarify the cause of biliary tract disease, endoscopic retrograde cholangiography is regarded as the technique of choice at this Medical Center. PTC is used in cases where the attempted endoscopic cannulation is unsuccessful (15–25 per cent), when the information obtained from ERC is incomplete, and finally, when visualization of the biliary tree is impossible by endoscopic technique, as in Case X. The difficulty in cannulating normal sized ducts by the percutaneous transhepatic technique is magnified in the evaluation of sclerosing cholangitis and associated diseases. Here the advantage of ERC is self evident.

SUMMARY

The ability to preoperatively diagnose the nature and extent of biliary tract disease has been significantly advanced with the advent of endoscopic retrograde cholangiography.

When supplemented with the appropriate use of percutaneous transhepatic cholangiography, many lesions of the biliary tract which heretofore were undiagnosed preoperatively can now be clearly defined.

The establishment of a diagnosis and related prognosis, as well as the providing of visual data upon which to plan a surgical approach are all benefits which attend these new diagnostic techniques.

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THE RENO-ALIMENTARY RELATIONSHIPS*

ANATOMIC-ROENTGEN STUDY OF THEIR CLINICAL SIGNIFICANCE

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MANY patients with renal disease present with symptoms which seem to arise from the digestive tract. Practically every case of urinary tract disease is known to be accompanied by some gastrointestinal complaint of a transitory or permanent character, particularly nausea, vomiting, epigastric distress, constipation, or diarrhea.[5] Gastrointestinal symptoms alone have been noted in up to 43 per cent of patients. Enlarged kidneys, particularly on the right, may not be clinically palpable. Radiologic investigation of such patients is often initiated by barium contrast studies. Characteristic effects upon specific portions of the bowel may first uncover the primary renal disease and redirect the course of evaluation appropriately.

The purpose of this report is to document the diagnostic changes in barium enema studies and upper gastrointestinal series secondary to a variety of renal diseases. It is based upon experience with 49 proved cases, including renal cysts and tumors (18 cases), renal ptosis and rotation (3 cases), invasion of bowel by hypernephroma (5 cases), perinephritis (5 cases), reno-alimentary fistulas (3 cases), and renal agenesis and ectopia (15 cases).

Basic to a roentgenologic appreciation of the characteristic bowel changes is an understanding of the reno-alimentary anatomic relationships.

ANATOMIC CONSIDERATIONS

The *right kidney* is in intimate relationship to two segments of the gastrointestinal tract, the descending duodenum and the hepatic flexure of the colon. Figure 1 illustrates these relationships and the reflections of the posterior parietal peritoneum in the right flank. Virtually all of the right kidney

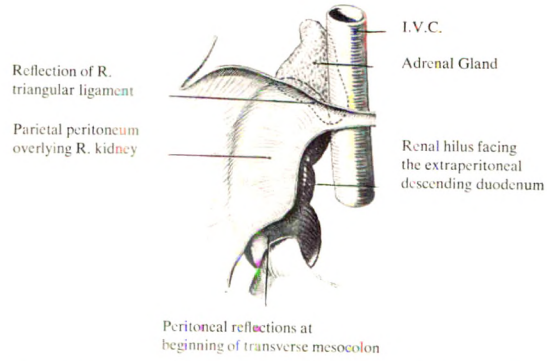

FIG. 1. Frontal drawing emphasizing relationship of right kidney to descending duodenum and hepatic flexure of the colon by virtue of their peritoneal reflections (after Corning[3]).

is invested anteriorly by peritoneum except at two sites constituting its "bare areas." Medially, the second portion of the duodenum descends immediately in front of the right kidney. Here, the peritoneum reflects to continue anterior to the duodenum and pancreas. Inferiorly, the extraperitoneal colon courses obliquely over the lower pole of the kidney. This occurs precisely at its level between (1) the distal ascending colon and the posterior hepatic flexure, which is related superiorly to the deep inferior visceral surface of the liver, and (2) the anterior hepatic flexure as it crosses the descending duodenum; it is this segment which marks the beginning of the trans-

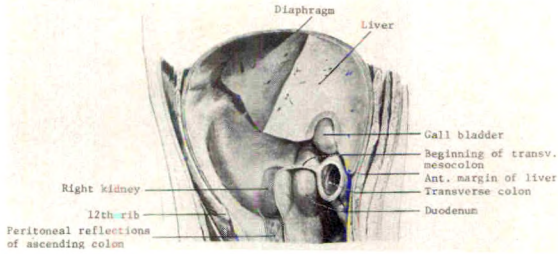

FIG. 2. Right parasagittal drawing showing anatomic relationships of the right kidney (after Corning[3]).

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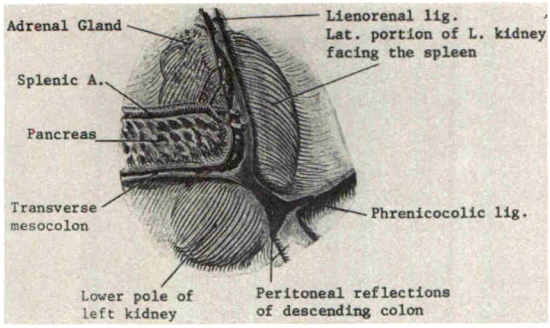


Fig. 3. Frontal drawing emphasizing relationship of left kidney to colon by virtue of their peritoneal reflections (after Corning[3]).

verse mesocolon and which is related superiorly to the gallbladder. Figure 2 clarifies these close relationships in a parasagittal dimension.

It is important to realize that a common variant exists in the extent of peritonealization of the second portion of the duodenum. Frequently, the postapical segment of the duodenum remains intraperitoneal for several cm. even as it courses inferiorly, suspended by the lesser omentum. The point at which it penetrates the posterior parietal peritoneum to descend extraperitoneally as a straight segment is characteristically marked by a mild junctional flexure. An

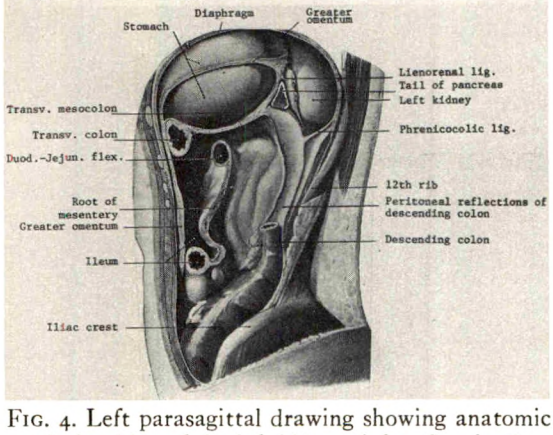


Fig. 4. Left parasagittal drawing showing anatomic relationships of the left kidney (after Corning[3]).

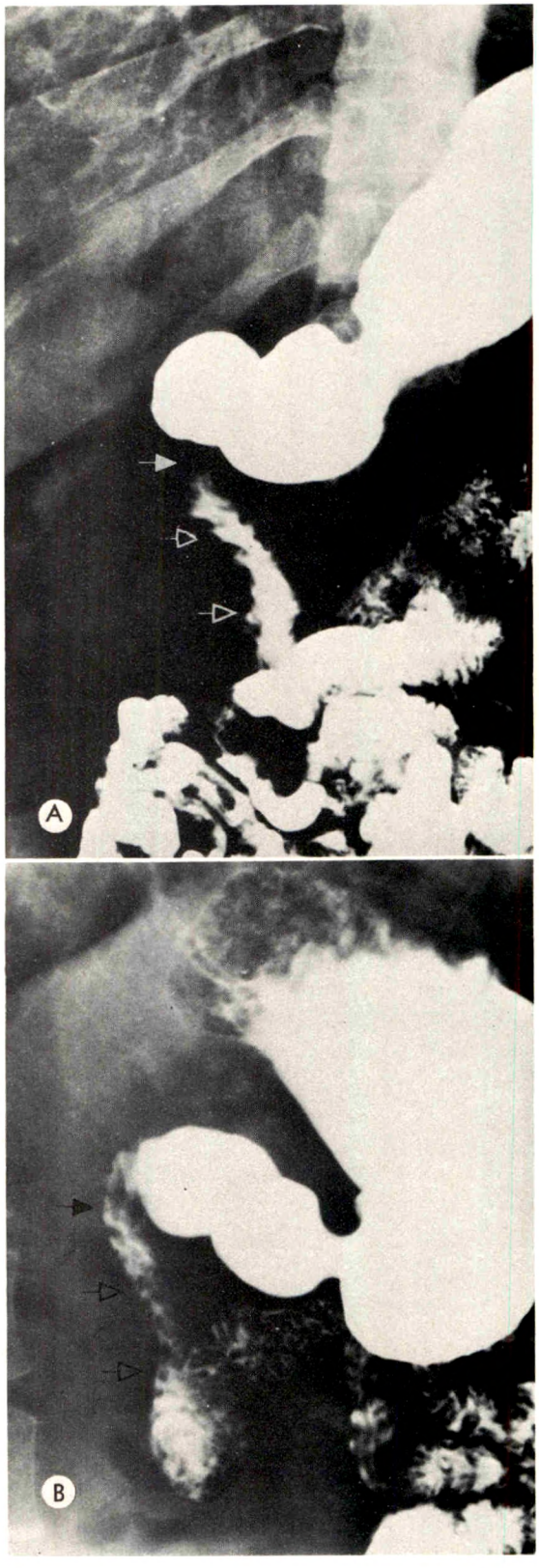


Fig. 5. *Displacement of descending duodenum by right renal cyst.* (*A*) Frontal and (*B*) right lateral views. The proximal portion descends normally (closed arrow), but there is medial and anterior displacement of the distal two-thirds (open arrows).

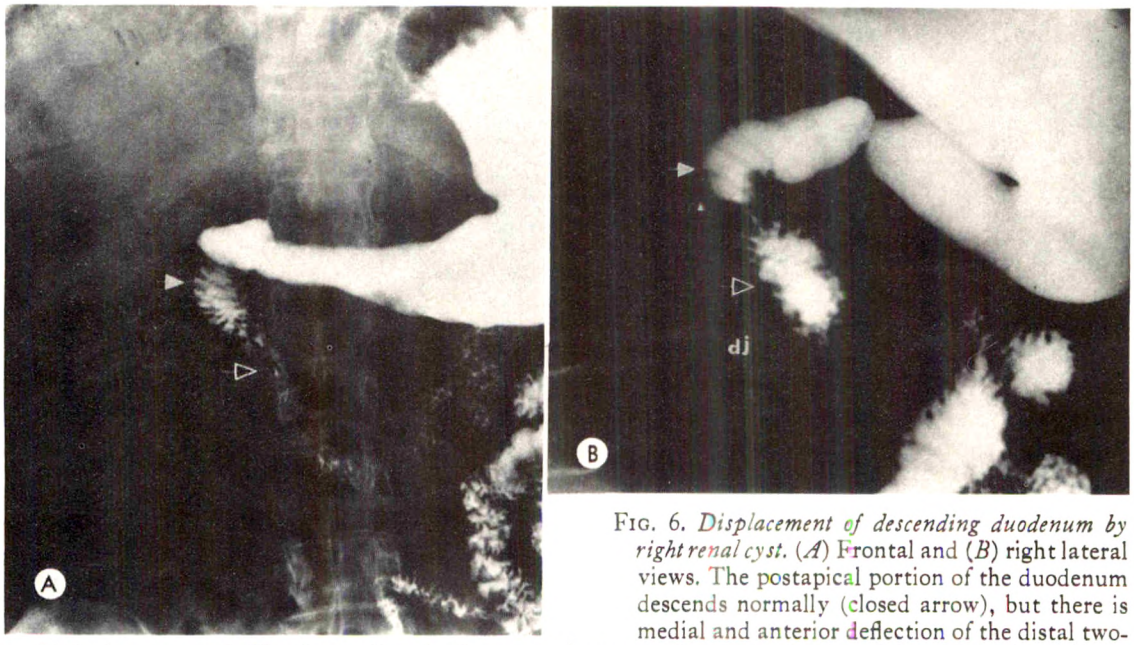


FIG. 6. *Displacement of descending duodenum by right renal cyst.* (*A*) Frontal and (*B*) right lateral views. The postapical portion of the duodenum descends normally (closed arrow), but there is medial and anterior deflection of the distal two-thirds (open arrow). The descending duodenum projects anterior to the duodeno-jejunal junction (dj). In *A*, note that the renal mass also causes elevation of the hepatic flexure of the colon.

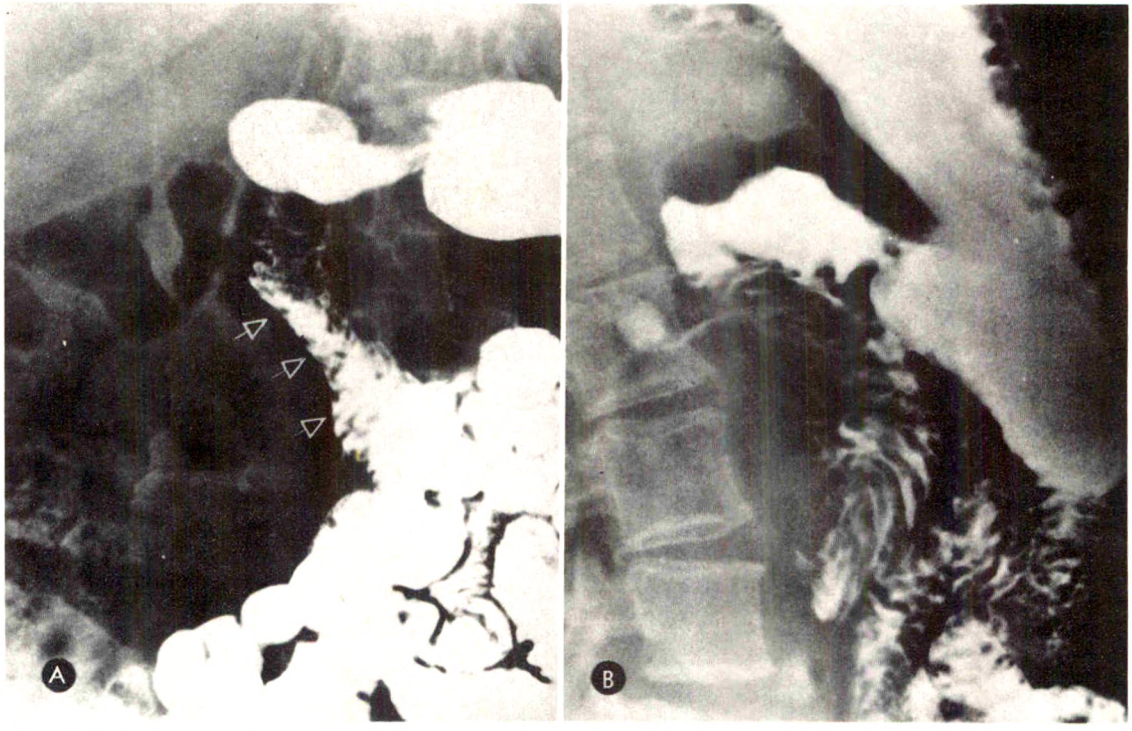


FIG. 7. *Displacement of descending duodenum by right renal cyst.* The proximal second portion of the duodenum descends normally. While (*A*) the posteroanterior projection shows only relatively mild medial displacement of the distal two-thirds with flattening of the mucosal folds laterally (arrows), (*B*) the lateral view demonstrates striking anterior bowing and extrinsic mucosal distortion. In *A*, note that the renal mass also causes elevation of the hepatic flexure of the colon.

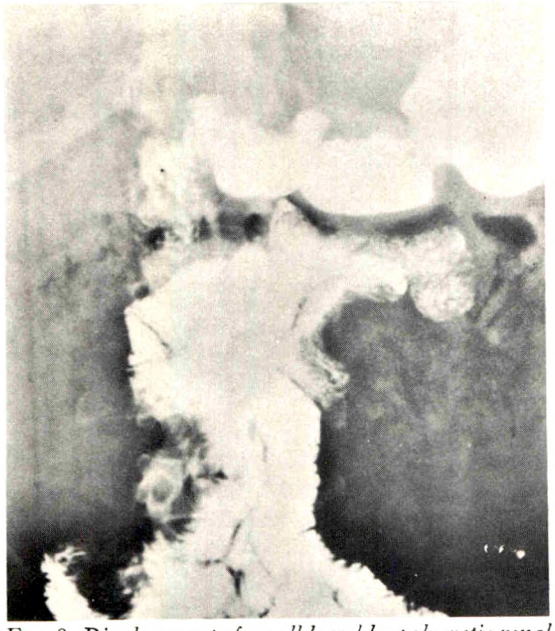
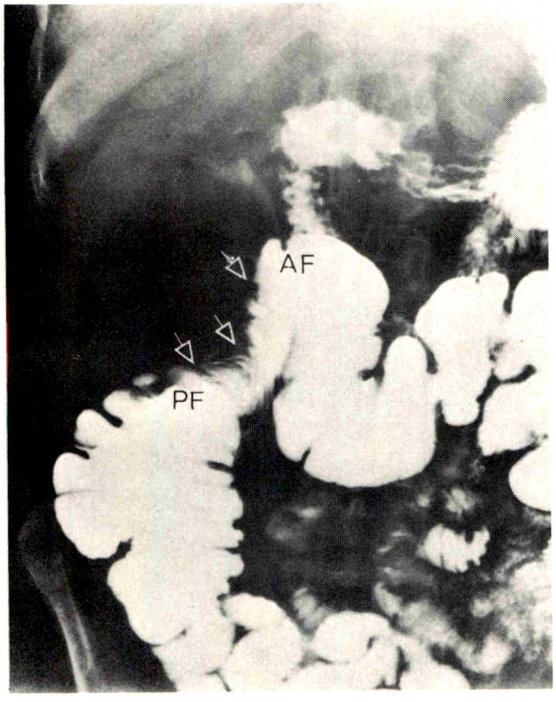


Fig. 8. *Displacement of small bowel by polycystic renal disease.* Massive renal enlargement bilaterally crowds jejunal loops toward the midline.

exaggerated form of this is seen as the "hammock" duodenum.

Because of the oblique position of the kidney along the lateral edge of the psoas muscle, its medial surface projects some-



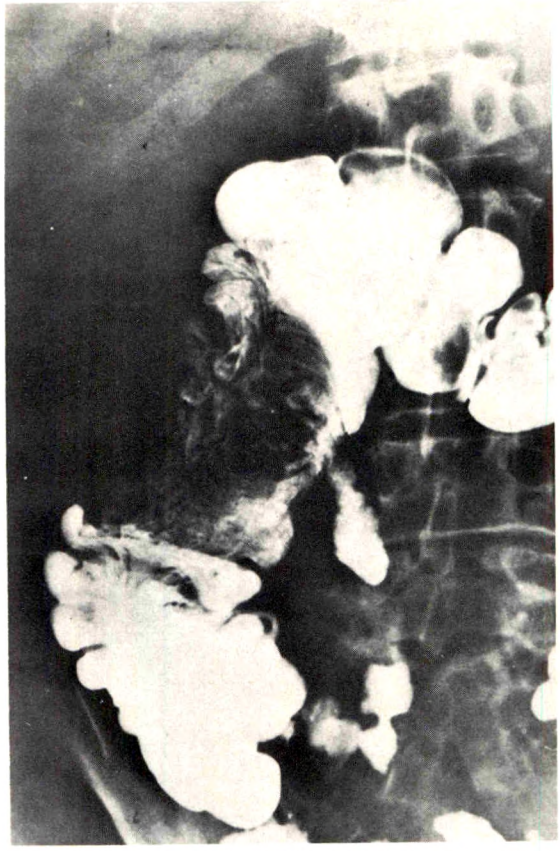


Fig. 10. *Displacement of right colon by hydronephrotic right kidney.* The segment between the two hepatic flexures is displaced inferiorly and medially. There is extrinsic flattening of its superior haustral border and marked compression of the lumen by the hugely dilated renal pelvis.

what anterior to its lateral border. It can thus be appreciated that both anterior and medial displacement of the descending duodenum, distal to its postapical segment, would result from a right renal mass.

While some variation occasionally exists, the descending duodenum usually lies on a

Fig. 9. *Displacement of right colon by right renal cyst.* The large intestine between the posterior (PF) and anterior (AF) hepatic flexures is displaced inferiorly and medially, with extrinsic compression of its superior haustral row (arrows). The posterior flexure is mildly displaced downward as the mass, originating in the middle third of the kidney, extends laterally into the flank. Note that there is no displacement of the descending duodenum.

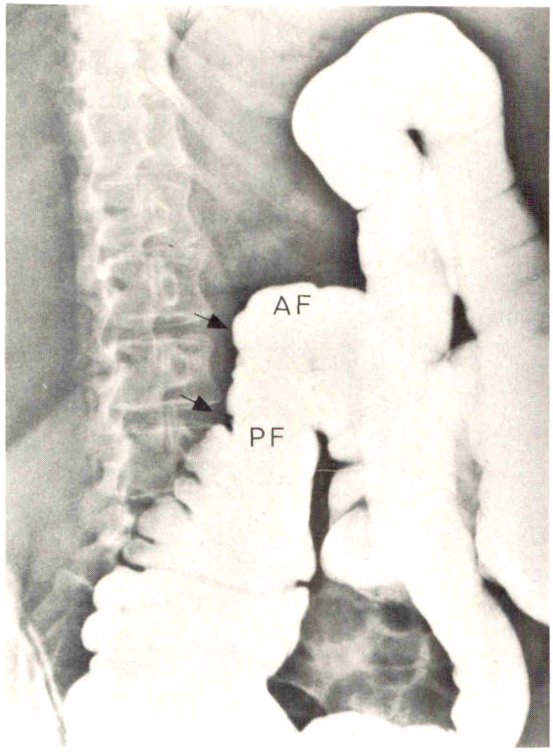


FIG. 11. *Displacement of right colon by right renal cyst.* Oblique view shows the large intestine between the posterior (PF) and anterior (AF) hepatic flexures displaced anteriorly and medially, with extrinsic flattening of its posterior haustral row (arrows).

more posterior plane than the duodenojejunal (dj) junction at the ligament of Treitz. In a standard right lateral projection of an upper gastrointestinal series, therefore, projection of the second duodenum anterior to the fourth (ascending) duodenum and dj junction should be viewed with suspicion of a right renal mass.

The upper two-thirds of the right kidney are related to the right colon between its two flexures, whereas the lower pole is intraperitoneal and is related laterally and anteriorly to the distal ascending colon.

The *right adrenal gland*, generally triangular in shape, faces the upper renal pole

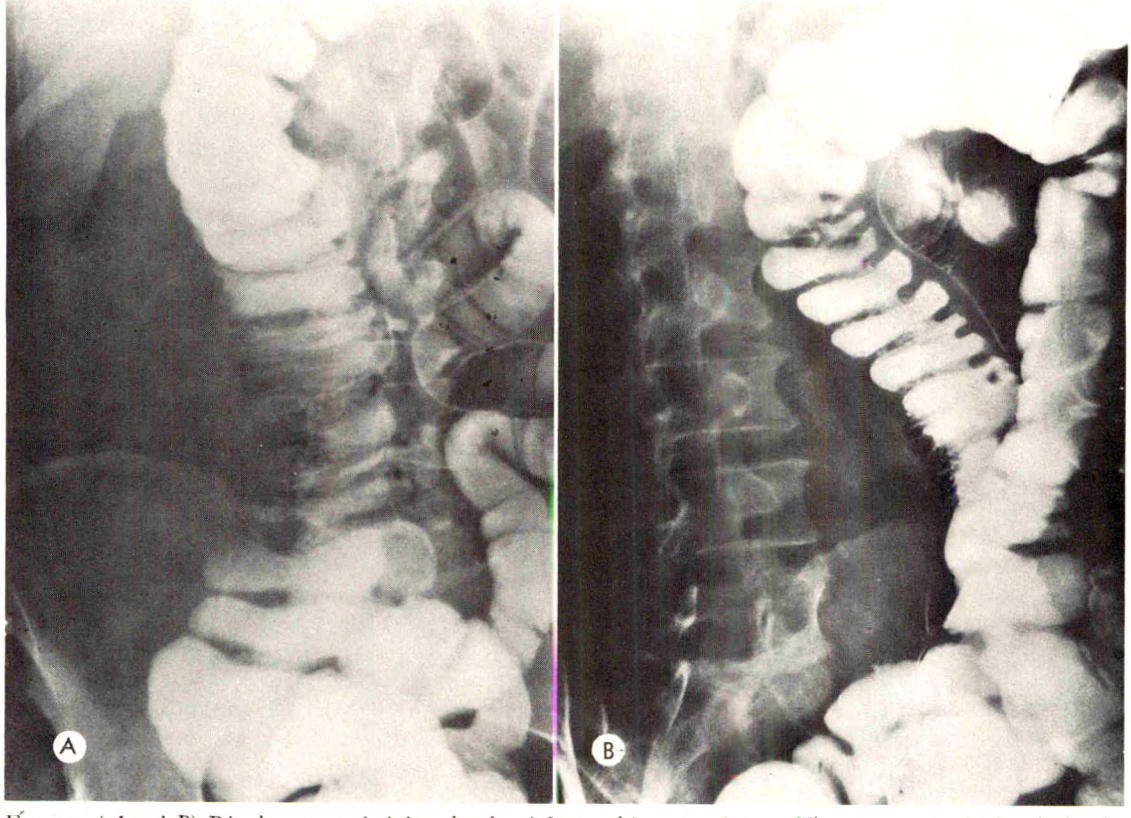


FIG. 12. (*A* and *B*) *Displacement of right colon by right renal hypernephroma.* The mass extends deeply in the flank and markedly displaces the ascending colon medially and anteriorly.

inferiorly (Fig. 1). Most of the gland is related anteriorly to the bare area of the liver, above the reflection of the right triangular ligament. A portion of it projects medially behind the inferior vena cava.

The relationships of the *left kidney* to bowel are most intimate to the distal transverse and proximal descending colon. Figure 3 illustrates these relationships and the complex peritoneal reflections in the left flank. The reflections of the transverse mesocolon cross the left kidney anteriorly along a narrow "bare area" at the junction of its middle and lower thirds to continue with the peritoneal reflections over the descending colon. At the junction of the transverse and the descending colon, the peritoneum reflects from the anatomic splenic flexure to form the phrenicocolic ligament which inserts on the left diaphragm at the level of the tenth and eleventh ribs. The distal transverse colon is related to the anterior surface of the lower half of the left kidney, although at variable distances depending upon the length of the transverse mesocolon. The lower pole is fully inframesocolic. The extraperitoneal descending colon passes downward along the lateral border of the left kidney, turning somewhat medially toward the lower border of the psoas muscle at the lower pole. Other peritoneal reflections account for the lienorenal ligament, within which the tail of the pancreas inserts. More anterior to the medial surface of the left kidney lie the greater curvature of the stomach, and inferiorly, the duodeno-jejunal junction and jejunal loops. Figure 4 clarifies these relationships in a parasagittal dimension.

The *left adrenal gland* is often semilunar in shape and extends anteriorly and medially over the upper renal pole (Fig. 3).

ROENTGENOLOGIC OBSERVATIONS

The intimate anatomic relationships of the kidneys to specific portions of the gastrointestinal tract precisely account for characteristic changes of deformity, displacement, or distortion.

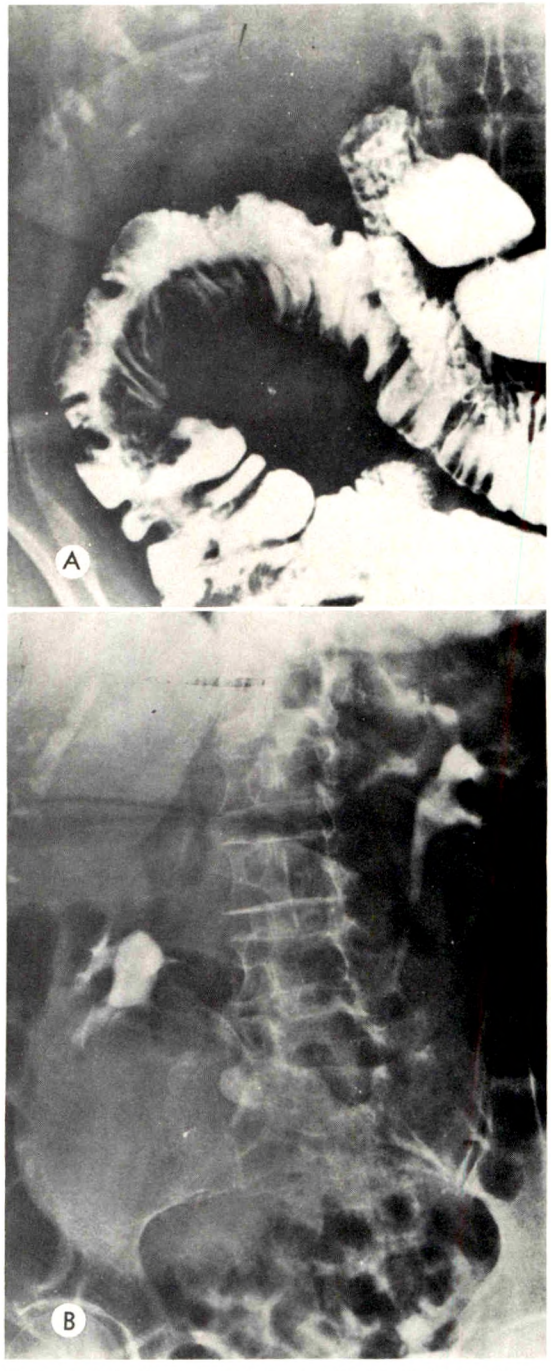


Fig. 13. *Displacement of right colon by right renal cyst.* (*A*) Superior displacement of segment between the two hepatic flexures, with extrinsic compression of its inferior haustral row. The mass also affects the ascending colon. The descending duodenum is uninvolved. (*B*) Excretory urogram documents a large mass in the lower renal pole with inframesocolic extension.

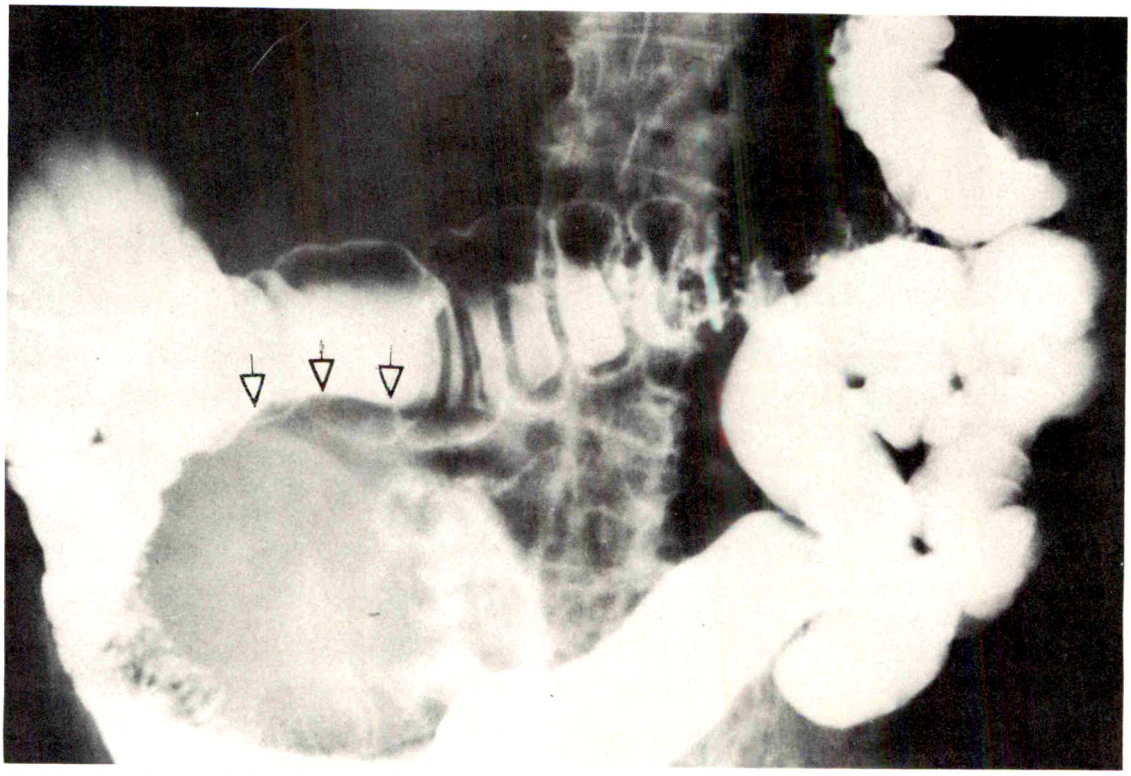
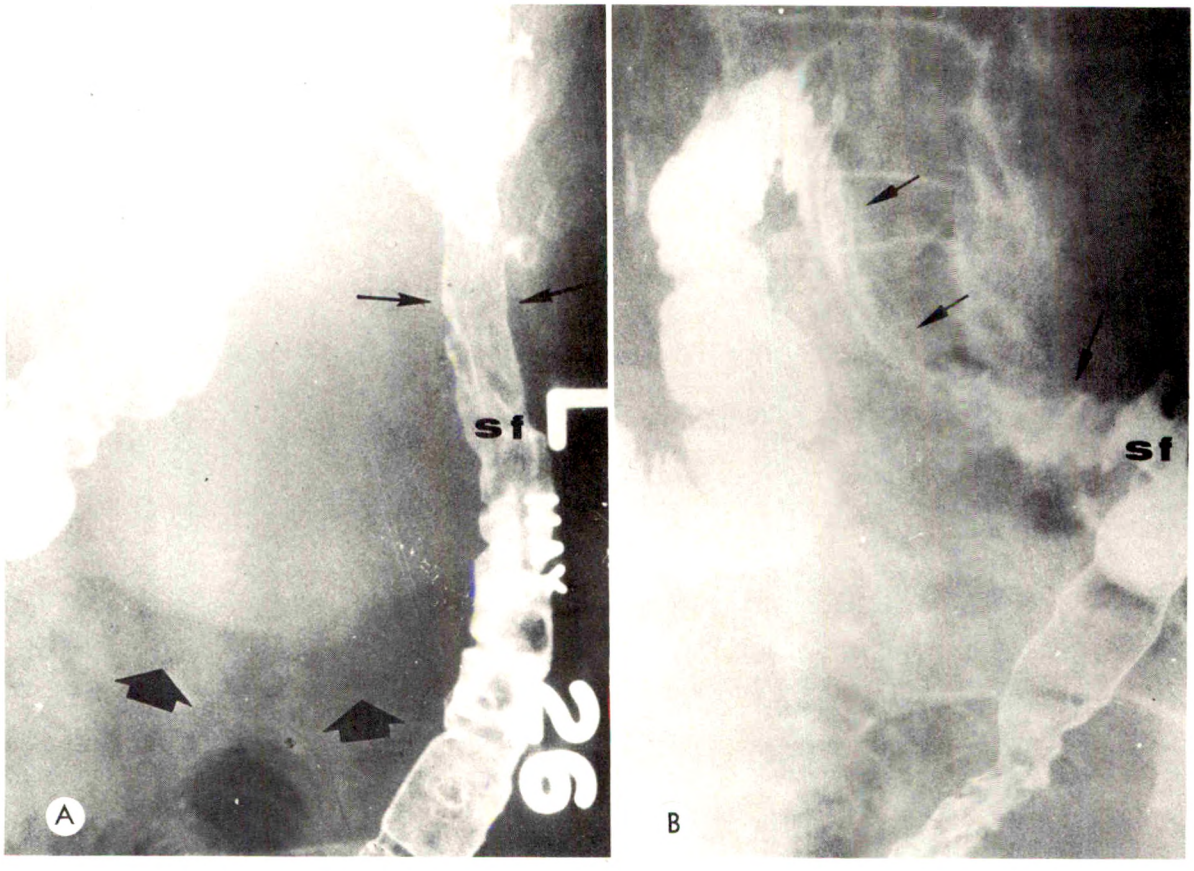


FIG. 14. *Displacement of right colon by right renal sarcoma.* There is mild extrinsic pressure upon the inferior border of the segment between the two hepatic flexures by the inframesocolic mass projecting from the lower renal pole. Note that the pressure effects can be localized particularly to the posterior haustral rows (arrows).



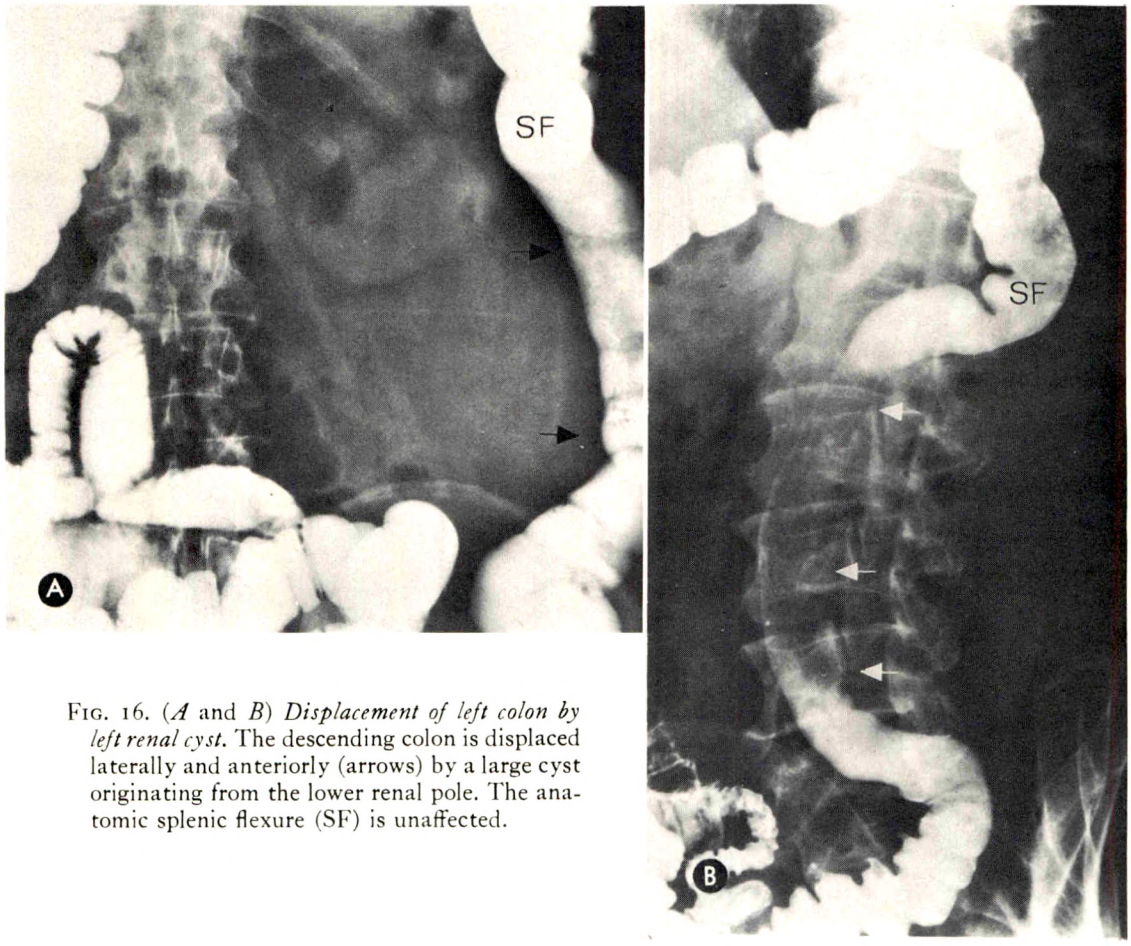


Fig. 16. (*A* and *B*) *Displacement of left colon by left renal cyst.* The descending colon is displaced laterally and anteriorly (arrows) by a large cyst originating from the lower renal pole. The anatomic splenic flexure (SF) is unaffected.

CHARACTERISTIC MASS DISPLACEMENTS

Right Kidney

Duodenum. Right renal masses typically cause medial and anterior displacement of the descending duodenum. The immediate postapical segment tends to be unaffected. This produces a characteristic appearance on frontal and lateral projections. In anteroposterior or posteroanterior views, the immediately proximal second portion of the duodenum descends vertically but the distal two-thirds is deflected medially (Fig. 5–7). In right lateral projections, correspondingly, the normal descent of the proximal segment is maintained but the distal portion is displaced anteriorly; this may result in a gentle axis inferiorly and anteriorly (Fig. 5*B*; and 6*B*) or in a striking ventral bowing (Fig. 7*B*). Extrinsic pressure on the mucosal folds themselves may be best appreciated in only one view. This may be shown as mass flattening of the normal mucosal contour undulations or gross mass distortion on the lateral or posterior wall.

Small Bowel. Massive kidney enlargement displaces jejunal loops anteriorly and inferiorly. With progression, particularly if

Fig. 15. (*A* and *B*) *Displacement of left colon by left renal cyst.* The anatomic splenic flexure (sf) is maintained, but there is lateral and anterior displacement of the descending limb of the distal transverse colon (arrows). The anteroposterior compression of its lumen is indicated also on the frontal view. The mass enlargement of the lower pole of the kidney is identifiable (large arrows).

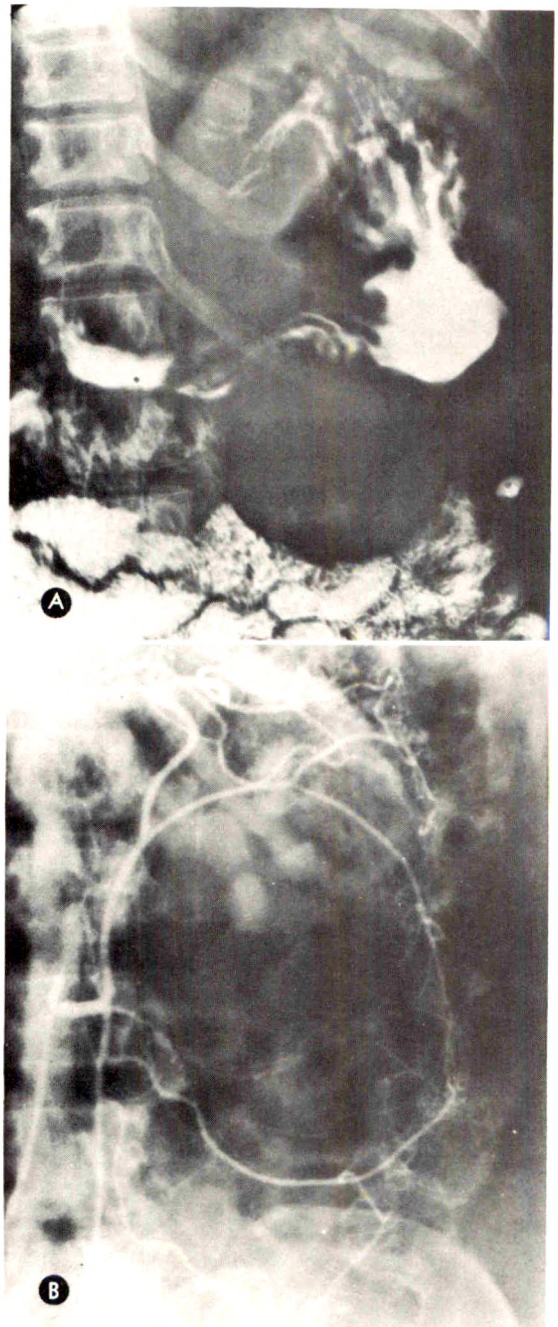


FIG. 17. *Displacement of stomach and small bowel by left renal cyst.* (*A*) The round mass elevates the greater curvature of the stomach and displaces the duodeno-jejunal junction medially and small bowel loops inferiorly. (*B*) Selective inferior mesenteric arteriogram shows arcuate displacement of the ascending left colic artery and its branches by the renal mass as it bulges through into the peritoneal cavity.

the process is bilateral as in polycystic renal disease, the small bowel may be crowded into the midline (Fig. 8).

Colon. In masses originating within the upper two-thirds of the right kidney, the right colon segment most typically involved is that extending between the posterior and anterior hepatic flexures. This demonstrates displacement inferiorly, medially, and anteriorly (Fig. 9–11). Extrinsic pressure may be further shown by flattening and compression of the superior (Fig. 9; and 10) and posterior (Fig. 11) haustral rows at this site. Extension of the mass laterally into the flank displaces the posterior hepatic flexure inferiorly (Fig. 9–11). Further progression may result in striking displacement of the ascending colon medially and anteriorly (Fig. 12). Maintenance of the lateral haustral contours (Fig. 12*A*) with extrinsic flattening of the posterior haustral sacculations (Fig. 12*B*) characterize the mass effects as extraperitoneal in site, rather than from a mass within the intraperitoneal lateral paracolic gutter.[9,10]

A mass originating in the lower pole of the right kidney characteristically elevates the colon between the two hepatic flexures (Fig. 13; and 14). Extrinsic compression occurs on the inferior haustral rows at this site, and the process may affect adjacent segments of the transverse and ascending colon. Oblique projections document that the affected colon is also usually displaced anteriorly and medially. At times, very discrete pressure changes selectively on the posterior haustra of this segment may be recognizable even on frontal projections (Fig. 14), an observation further indicating the extraperitoneal nature of the mass.[10]

Left Kidney

Colon. Left renal masses come into relationship to the colon usually before they attain a size to displace the stomach, dj junction, or small bowel. Masses arising in the upper half may displace the distal transverse colon inferiorly and anteriorly. Those originating in the lower half are often first

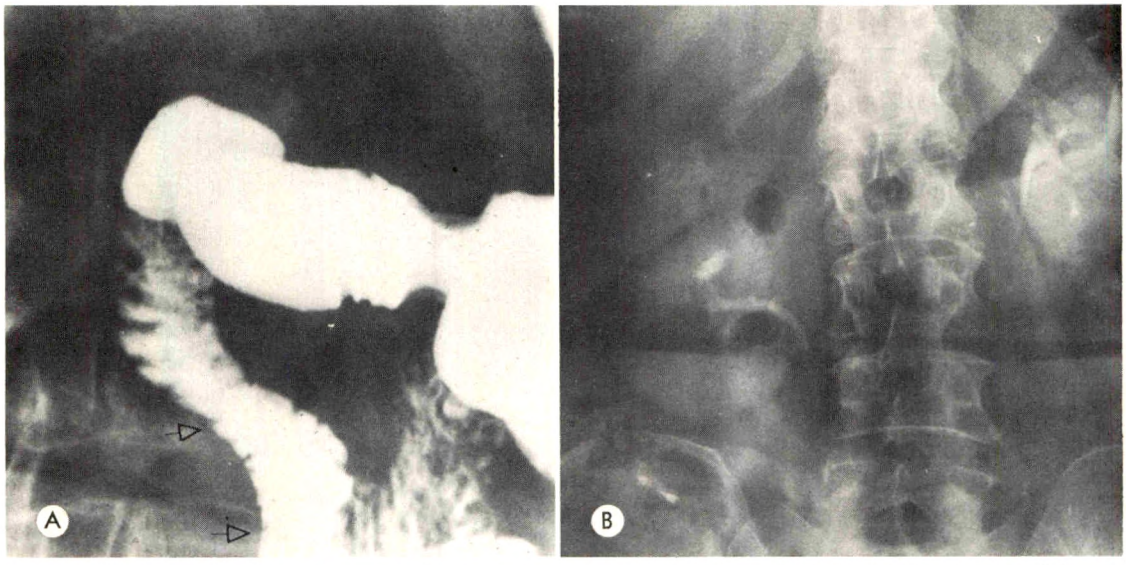


Fig. 18. *Displacement of the descending duodenum by a ptotic right kidney.* (*A*) The distal segment of the descending duodenum is displaced anteriorly and medially (arrows). (*B*) Intravenous pyelogram shows a ptotic right kidney with rotation about its vertical axis.

revealed by typical effects upon specific portions of the left colon. The descending limb of the distal transverse colon appears compressed and displaced laterally and anteriorly (Fig. 15, *A* and *B*). Significantly, the landmark of the anatomic splenic flexure is preserved. Masses projecting from the lower pole displace the descending colon laterally and anteriorly (Fig. 16). Again, the anatomic splenic flexure is unaffected.

Stomach and Small Bowel. A left renal mass may bulge through into the peritoneal cavity, as shown in Figure 17, *A* and *B*, to displace the greater curvature of the stomach and jejunal loops.

PTOSIS AND ROTATION

Ptotic descent of the kidney is frequently accompanied by rotation about its vertical axis. The condition is commoner on the right where its effects upon the bowel may be misleading unless the anatomic relationships are recognized. The distal descending duodenum may be displaced medially and anteriorly in a manner indistinguishable from a true renal mass (Fig. 18, *A* and *B*). The ptotic kidney may further descend fully to the inframesocolic right lower quadrant so that, with rotation, it displaces primarily small bowel loops (Fig. 19, *A* and *B*).

INVASIVE HYPERNEPHROMA

Renal neoplasms may directly invade adjacent segments of bowel, possibly as recurrences many years after resection of the primary tumor. With growth, they tend to produce bulky intraluminal masses without significant obstruction since they generally elicit no desmoplastic response.[8] Occasionally, however, we have found that they may produce luminal narrowing with mucosal destruction simulating a primary carcinoma of the bowel (Fig. 20, *A* and *B*). Recognition of the usual sites of involvement and identification of any extraluminal soft-tissue mass lead to the correct diagnosis. On the right, the descending duodenum and, on the left, the distal transverse colon or proximal descending colon (Fig. 21, *A* and *B*) are mostly commonly involved.

PERINEPHRITIS AND RENO-ALIMENTARY FISTULAS

Advanced perirenal infection may break through fascial boundaries to involve overlying bowel. The pathogenesis involves a

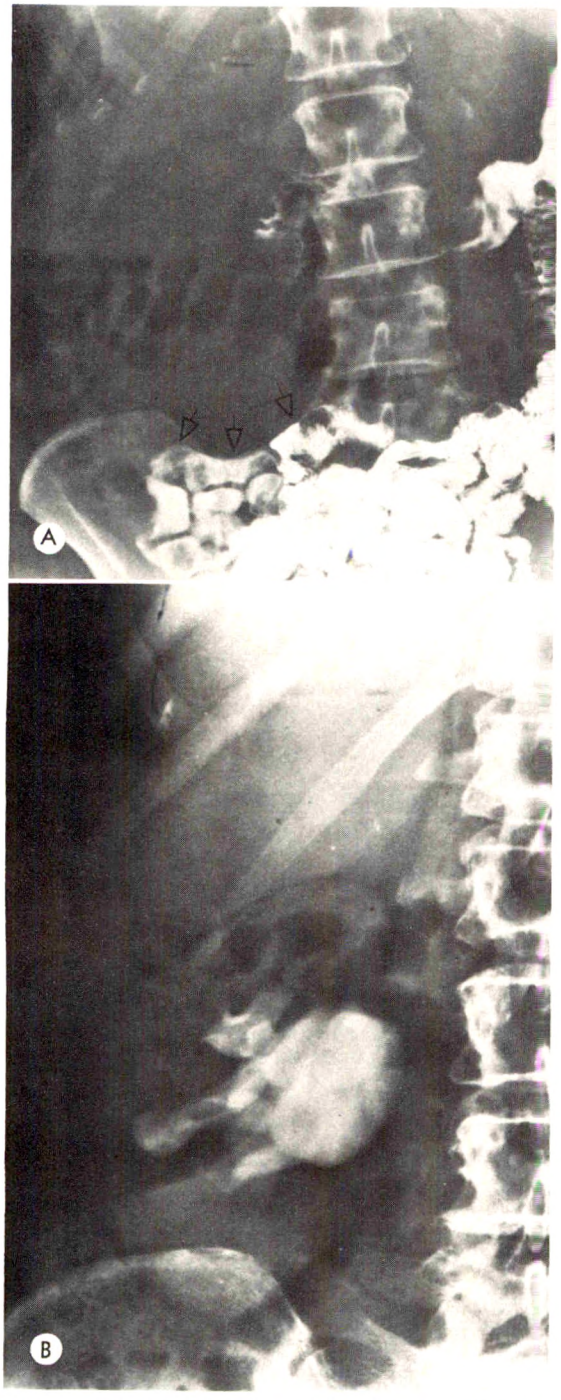


FIG. 19. *Displacement of small bowel by a ptotic right kidney.* (*A*) There is gentle arcuate displacement of ileal loops (arrows) by a soft tissue right lower quadrant mass. (*B*) Intravenous pyelogram shows a hydronephrotic, ptotic right kidney.

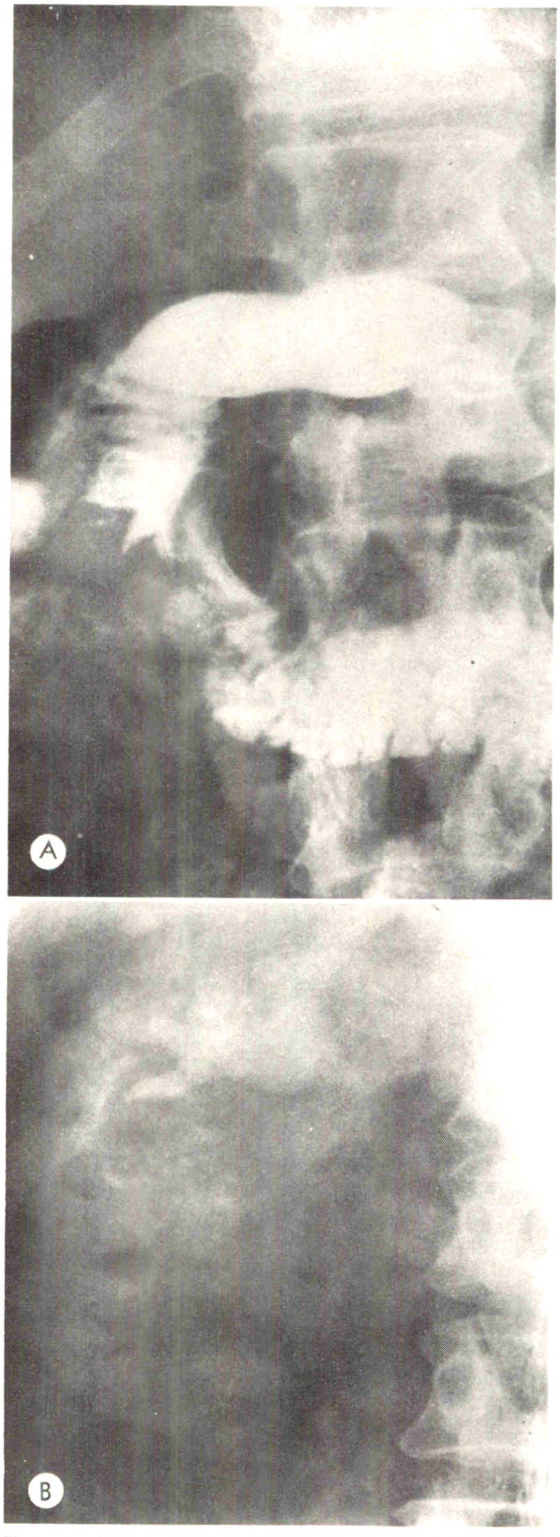


FIG. 20. *Direct invasion of the descending duodenum by right renal hypernephroma.* (*A*) Mucosal destruction simulates a primary neoplasm of the duodenum. (*B*) Excretory urogram shows large mass with a few faint calcifications within the lower pole of the right kidney, displacing the collecting system. (*A* reproduced with permission of *Radiology*.[8])

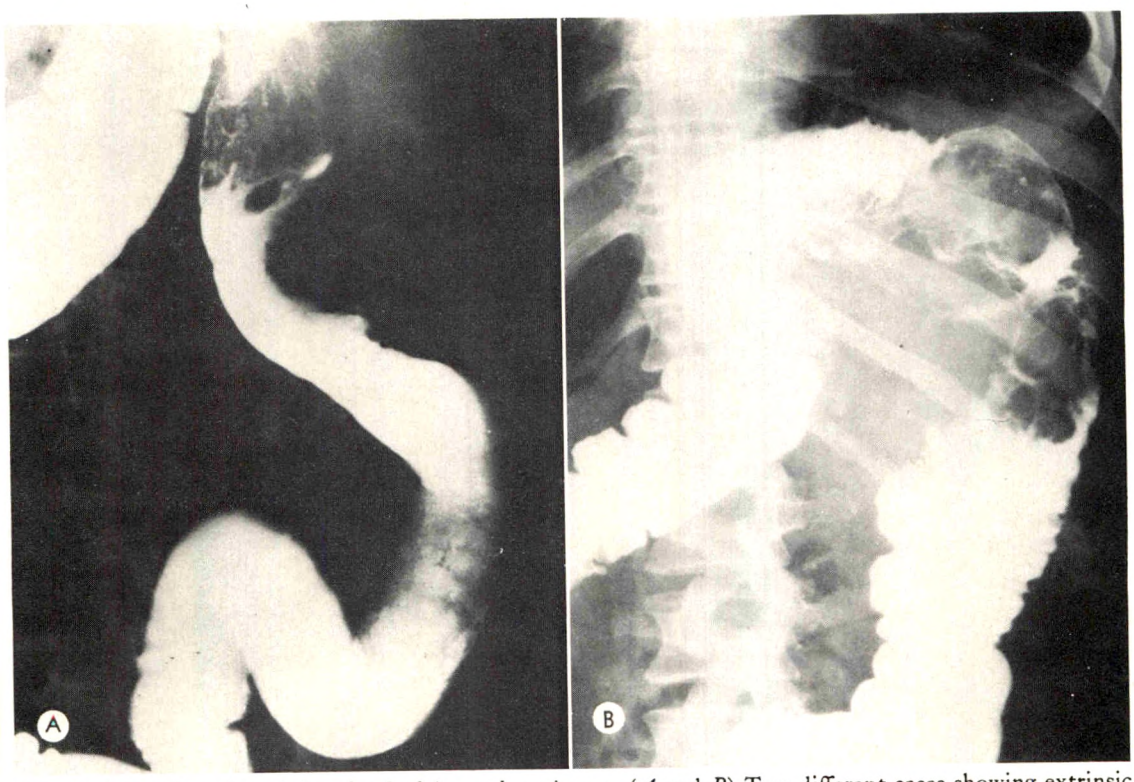


Fig. 21. *Direct invasion of the colon by left renal carcinoma.* (*A* and *B*) Two different cases showing extrinsic and intramural masses of the distal transverse and proximal descending colon with bulky polypoid intraluminal extensions.

site of renal infection which breaks through the capsule of the kidney to contaminate the perirenal space. Colonic changes secondary to left perinephritis have recently been reported,[7] affecting the distal transverse colon and particularly the segment distal to the anatomic splenic flexure. The perirenal abscess tends to localize in the rich fat dorsolateral to the lower renal pole. Changes reflecting at least inflammatory adherence affect principally the medial or posterior contour of the descending colon or they may be circumferential. They are manifested primarily by spastic narrowing or scalloped induration. A gross extraperitoneal sinus communication represents advanced transmural erosion. Most reno-alimentary fistulas are secondary to an underlying kidney infection which establishes communication usually with the descending duodenum or left colon. Bissada and associates[1] collected 92 cases from the literature. The most common lesions were renocolic and renoduodenal fistulas. Rarely, the communication may be due to a primary process of the bowel (Fig. 22, *A–D*).

Renal Agenesis and Ectopia

It has recently been shown that agenesis or ectopia of the kidney is frequently accompanied by characteristic malposition of specific portions of the bowel.[11] On the right, the descending duodenum and proximal jejunal loops and on the left, the distal transverse colon and anatomic splenic flexure (Fig. 23, *A* and *B*; and 24) may occupy the area of the renal fossa. The colonic malposition may be evident as a plain film finding (Fig. 24). Renal ectopia, particularly in the iliac fossa or lower abdomen, may result in a characteristic mass effect upon or displacement of the ascending or descending colon. These observations are of clinical significance both in uncovering the

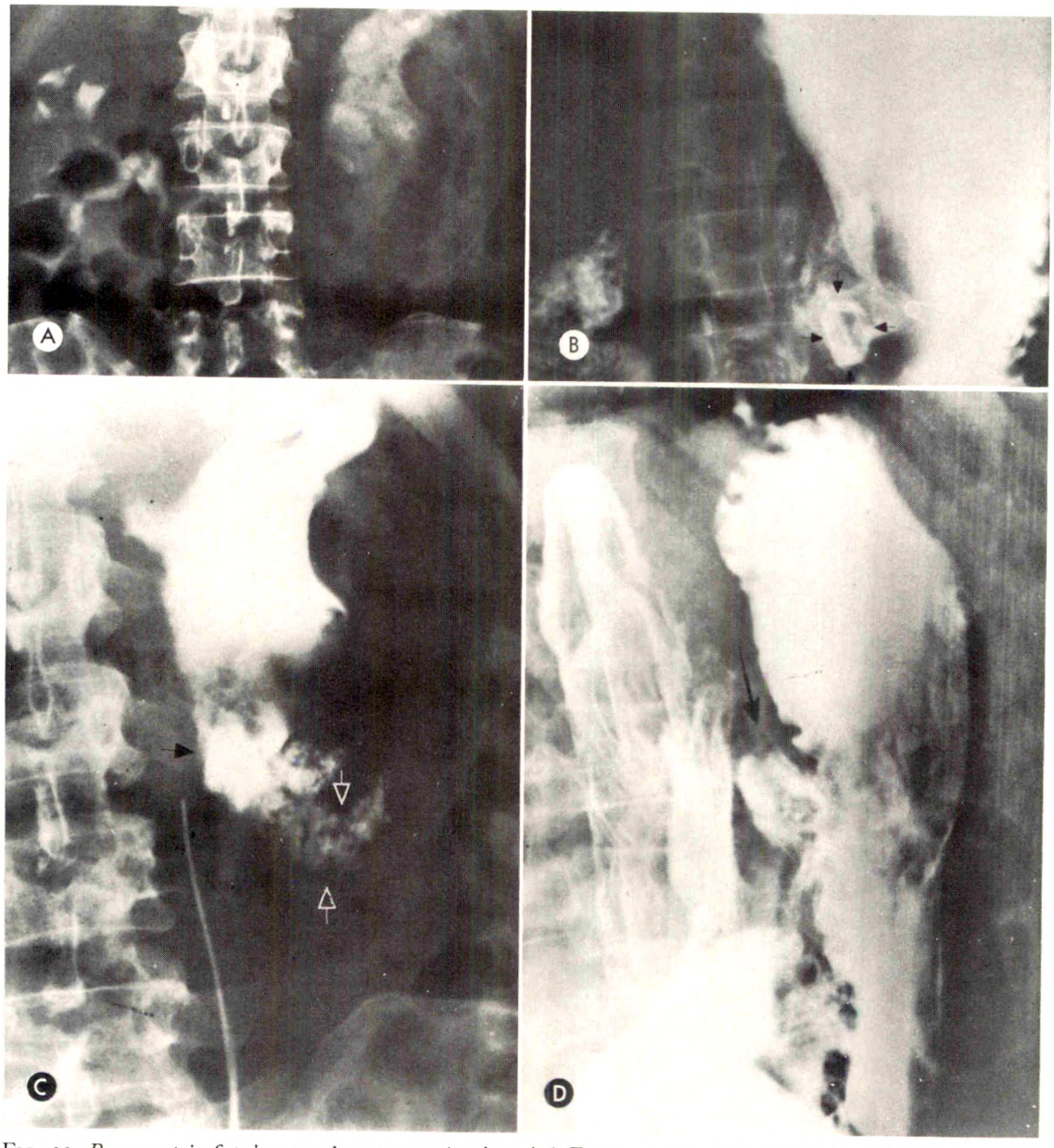


FIG. 22. *Reno-gastric fistula secondary to gastric ulcer.* (*A*) Excretory urogram. Gross chronic inflammatory changes with distorted collecting system on the left. (*B*) Retrograde pyelogram. Loculated extravasation (black arrow) with opacification of gastric mucosa (white arrows). (*C* and *D*) Upper gastrointestinal series documents large ulcer on posterior wall of stomach (arrows) penetrating to the left kidney. (Courtesy of Arthur Lieber, M.D., Department of Radiology, University of Kentucky Medical School, Lexington, Kentucky.)

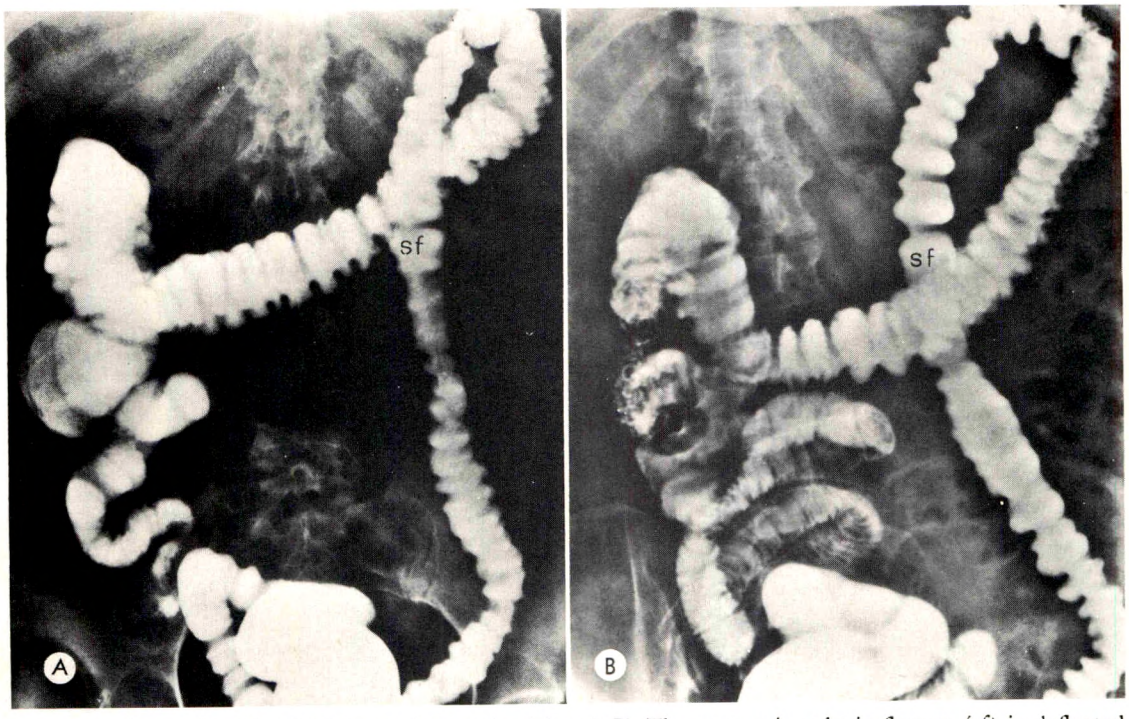


Fig. 23. *Colon malposition in left renal agenesis.* (*A* and *B*) The anatomic splenic flexure (sf) is deflected medially and posteriorly, occupying the position of the "empty" renal fossa.

renal anomaly and in distinguishing these bowel changes from such conditions as internal hernia, malrotation of the intestines, and displacement by a tumor mass or splenomegaly.

DISCUSSION

The frequent nonspecificity of symptoms due to urinary tract disease and the general inaccessibility of the kidneys to physical examination often lead to roentgenologic investigation being initiated by barium contrast studies of the bowel. The kidneys are in intimate anatomic relationship to specific portions of the gastrointestinal tract. Identification of bowel alterations as a consequence of underlying renal disease immediately directs the course of the diagnostic evaluation and, in certain instances, demonstrates the extent of the disease. Only limited observations concerning such effects of renal masses have been made in the past. Bluth and Vitale[2] reported 6 cases of right renal enlargement producing changes, chiefly anterior displacement, in the roentgen appearance of the descending duodenum. Appreciation of the intimate reno-alimentary anatomic relationships is essential to an understanding of the bowel changes in not only renal masses, but also in cases of extensive perirenal infections and fistulas, invasion by occult or recurrent hypernephroma, renal ptosis and rotation, and the congenital anomalies of renal agenesis and ectopia.

SUMMARY

The intimate anatomic-roentgen relationships of the kidneys to specific portions of the gastrointestinal tract are detailed.

Characteristic effects on barium contrast studies may first uncover primary renal disease, demonstrate its extent, and redirect the course of diagnostic evaluation.

The specific bowel changes secondary to renal masses, renal ptosis and rotation, invasive hypernephroma, perinephritis, reno-

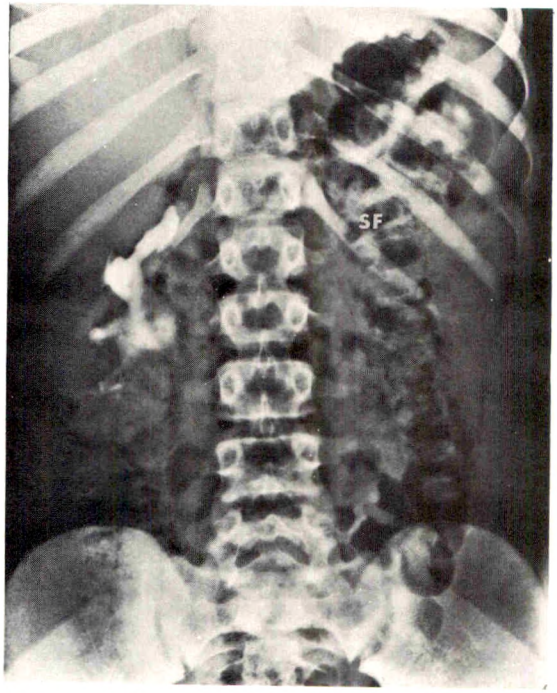


FIG. 24. *Colon malposition in left renal agenesis.* Excretory urogram. In this child, the anatomic splenic flexure (SF) occupies the "empty" renal fossa. There is compensatory hypertrophy of the right kidney.

alimentary fistulas, and renal agenesis and ectopia are described and illustrated.

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VOL. 123, NO. 2

RADIOISOTOPE SCINTIGRAPHY IN DIAGNOSIS OF BARRETT'S ESOPHAGUS*

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ROCHESTER, MINNESOTA

IN 1950, Barrett[2] first described a condition in which the lower esophagus was lined with columnar epithelium resembling that of the stomach, instead of the normal stratified squamous epithelium. Morphologically, the epithelium in Barrett's esophagus contains mucus-secreting goblet cells, enterochromatin cells, and, in about one-half of the cases, parietal cells.[1,5,6,8,9,14,15] Diagnosis of this entity may be strongly suspected roentgenographically by the combination of mid-esophageal stricture and esophageal hiatal hernia together with normal esophageal motility, except at the level of the stricture.[12] Mucosal electrical potentials and esophageal motility have also been studied in attempts to diagnose Barrett's esophagus.[1,6,14] Although these various techniques may suggest this condition, the diagnosis must currently be confirmed by endoscopic biopsy. We report a new approach to the diagnosis of Barrett's esophagus, which is based upon the principle that radioactive (Tc^{99m}) pertechnetate is selectively taken up by the gastric type of mucosa found in Barrett's esophagus and that it can be visualized by scintigraphic imaging.[3,4,7,10,11]

MATERIAL AND METHOD

Patients suspected of having Barrett's esophagus were studied with radioisotope scintigraphy, conventional barium roentgenography, and endoscopy plus biopsy. They were selected for study if all of the following criteria were satisfied: (1) clinical symptoms of esophagitis or dysphagia; (2) roentgenographic evidence of stricture of the esophagus, with or without associated esophageal hiatal hernia; and (3) ulceration of the esophagus, with or without stricture.

Technique of Radioisotope Scintigraphy. The fasting patient is given 5 mci Tc^{99m} pertechnetate intravenously. No perchlorate or other blocking agent is used. Because the isotope is secreted into saliva (as well as into gastric juice), the patient is instructed not to swallow between the time of injection and termination of the procedure; this is facilitated by use of a dental type of oral aspirator. The patient stands during the examination in order to lessen the possibility of reflux of contents from the stomach into the esophagus, and is placed in front of the gamma camera (Searle, model HP) with his arms resting on it to minimize motion. Scintigraphic imaging is performed at 30 and 60 minutes following injection; these intervals allow the isotope concentrations in the blood pool to diminish. For each image, 600,000 counts are accumulated. After the scan, the patient swallows barium and a roentgenogram is taken in the upright position. This serves to define better the location of the roentgenographic esophagogastric junction for comparison with the scintigrams, which are made in the same position.

RESULTS

The appearance of the scintigram in the normal subject is seen in Figure 1, which demonstrates not only intense concentration of isotope by the stomach but also the lack of radionuclide uptake by the esophagus. Evidence of activity is also seen in the cardiac blood pool.

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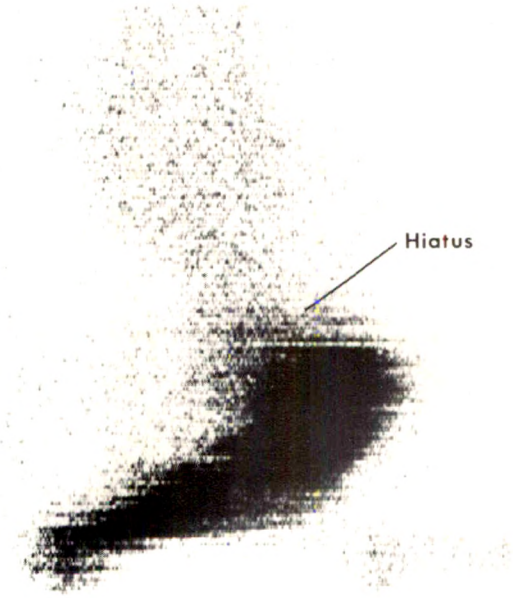

FIG. 1. Tc^{99m} pertechnetate scan of the upper abdomen and lower thorax in normal subject. The isotope is concentrated in the gastric mucosa, but there is no uptake above the esophagogastric junction. A small amount of isotope remains in the cardiac pool. (Reproduced with permission from *Mayo Clin. Proc.*[4])

Figure 2, *A* and *B*, demonstrates the characteristic roentgenographic and scintigraphic features of Barrett's esophagus. The roentgenogram shows an esophageal hiatal hernia and a stricture of the mid-esophagus. In this particular patient, fluoroscopy showed the peristaltic wave passing through the stricture, with only slight hesitation at the level of the stricture, and then its continuation down to the upper margin of the hernia, considered to be the roentgenographic esophagogastric junction. The scintigram in Figure 2*B* shows uptake of activity by the stomach with continuous concentration of the isotope up the esophagus to a level that corresponds approximately to that of the stricture on the adjacent roentgenogram; this indicates extension of the gastric mucosa up the esophagus to the level of stricture.

We studied 6 patients with Barrett's esophagus, in all of whom ectopic gastric mucosa in the lower esophagus was proved histologically. All patients were men whose ages ranged from 37 to 69 years. Dysphagia

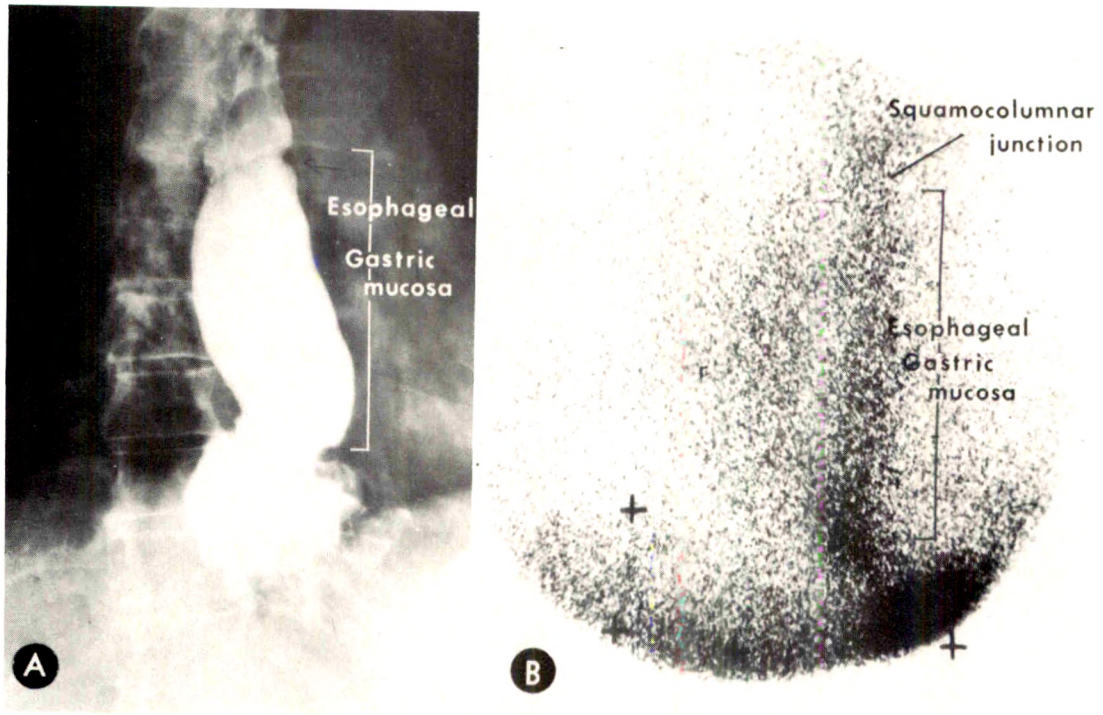

FIG. 2. (*A*) Barium swallow and (*B*) Tc^{99m} pertechnetate scan in patient with Barrett's esophagus. Uptake of isotope extends cephalad beyond the esophagogastric junction to the level corresponding to stricture on the roentgenogram.

and heartburn were the most common presenting complaints.

REPORT OF CASES

Case I. A 56 year old man was referred because of a 5 year history of nocturnal heartburn; he experienced a burning retrosternal pain when supine. This was relieved by sitting up, sleeping with the head of the bed elevated, and by taking antacids. The history was otherwise normal. Results of the physical examination were unremarkable. Fluoroscopically, a stricture of the mid-esophagus was observed. The stripping wave was noted to pass through the stricture and down to the level of the hiatus, where the roentgenologic esophagogastric junction was located. Scintigraphy with Tc^{99m} pertechnetate showed that the isotope concentrated in the stomach, with continuous extension of uptake cephalad in the esophagus to the approximate level of the roentgenographic stricture (Fig. 3, *A* and *B*). Biopsy specimens taken just below the level of the stricture all demonstrated gastric mucosa, except for the absence of parietal cells.

Case II. A 59 year old man had noted dysphagia for the previous 6 months. He had noted that solid foods gradually began to stick in what seemed to be the upper esophagus; he had also felt pain in the retrosternal region for a short period, until the food appeared to continue down the esophagus, but he had no difficulty with liquids and had not experienced vomiting after eating. There had apparently been no weight loss or melena. Fluoroscopically, there was stricture of the mid-esophagus and the esophagogastric junction was determined to be at the level of the hiatus. Isotope scintigraphy demonstrated uptake of Tc^{99m} pertechnetate by the stomach with continuous uptake by the wall of the lower esophagus to a level corresponding to that of the stricture on the roentgenogram (Fig. 4, *A* and *B*). Biopsy taken just below the level of the stricture demonstrated columnar epithelium; as in Case I, parietal cells were absent.

Case III. A 69 year old man had a 1 year history of progressive difficulty in swallowing solid foods. Dysphagia only occurred with solid foods but his symptoms were becoming more frequent. He had no difficulty in swallowing liquids and no other symptoms. Results of the physical examination were unremarkable. Fluoroscopically, there was a stricture of the mid-esophagus with no associated esophageal hiatal hernia; the esophagogastric junction was

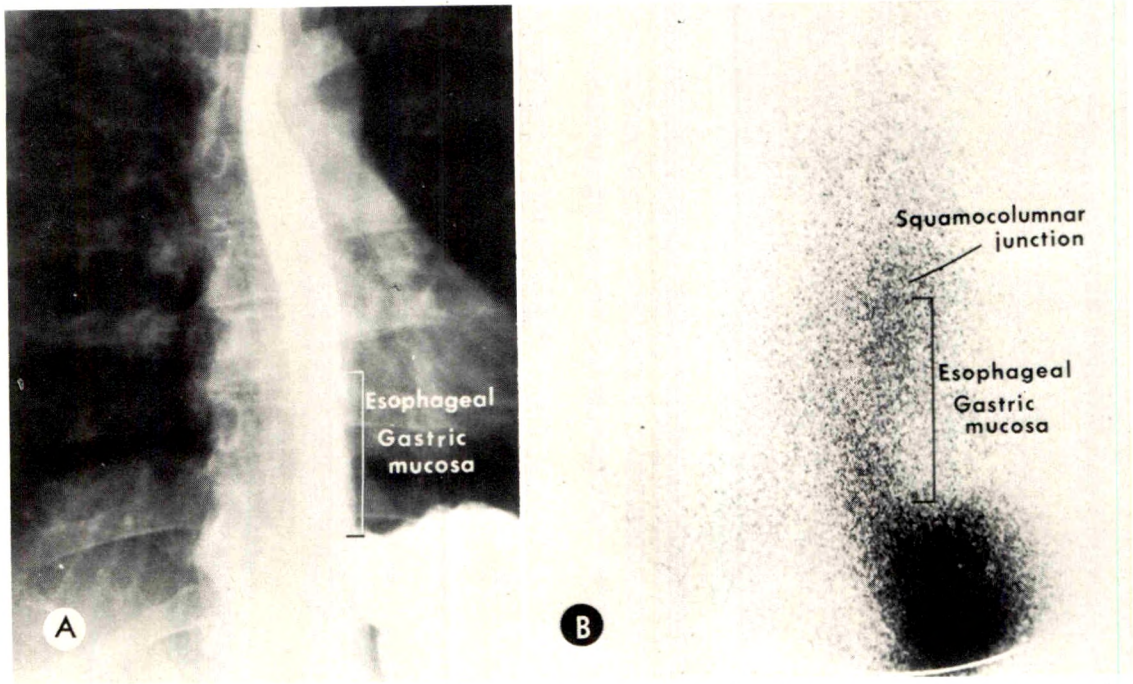

Fig. 3. Case I. (*A*) Barium swallow and (*B*) Tc^{99m} pertechnetate scan. Scintigram demonstrates concentration of isotope in lower esophagus to the level corresponding to stricture on the roentgenogram.

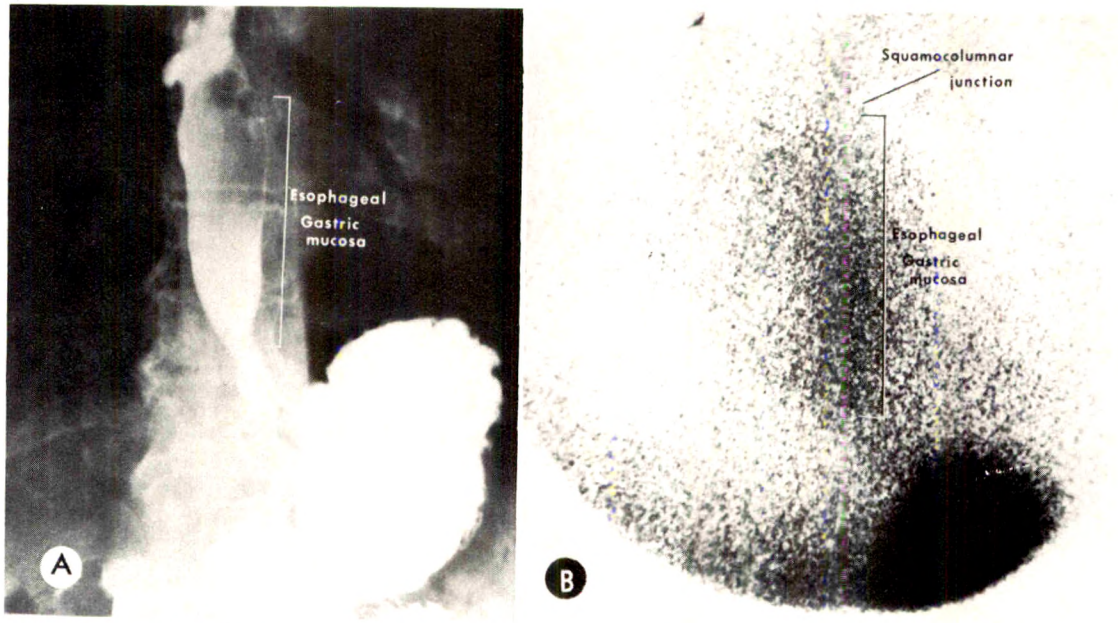

Fig. 4. Case II. (*A*) Barium swallow and (*B*) Tc^{99m} pertechnetate scintigram. Uptake of isotope extends above the esophagogastric junction to the level comparable to esophageal stricture on the roentgenogram.

determined to be at the level of the hiatus. Radioisotope scintigraphy demonstrated uptake, both by the stomach and by the esophagus, to a level that corresponded to the level of the stricture on the roentgenogram (Fig. 5, *A* and *B*). Biopsy taken immediately below the level of the stricture demonstrated gastric type mucosa (Fig. 6).

Case IV. A 62 year old man, who complained of nervousness and depression, had noted retrosternal burning for 9 years; at that time an esophageal hiatal hernia had been detected and repaired surgically. Despite the surgical intervention, recurrent pyrosis developed, increasing during the 2 years before the current examination. The patient had also noted tarry stools on several occasions. The results of physical examination were unremarkable. Fluoroscopic examination demonstrated an esophageal hiatal hernia and a stricture of the mid-esophagus. Scintigraphy with Tc^{99m} pertechnetate revealed concentration of the isotope by the stomach and extension cephalad into the esophagus to a level corresponding to that of the stricture seen on the roentgenogram (Fig. 7, *A* and *B*). Biopsy specimens taken just below the level of the stricture revealed gastric type of columnar epithelium with no parietal cells.

Case V. A 37 year old man presented with heartburn and dysphagia. An esophageal hiatal hernia was found, and this was repaired after medical evaluation. In the course of postoperative follow-up the patient noted continued symptoms of heartburn. Fluoroscopy demonstrated a stricture of the esophagus at the level of the aortic arch; the esophageal peristaltic wave passed through the stricture and continued down the esophagus to the hiatus. Scans with Tc^{99m} pertechnetate revealed uptake of the isotope in the esophagus to the level of the stricture as seen on the roentgenogram (Fig. 8, *A* and *B*). The delayed scan was obtained 4 hours after injection in this case, instead of the usual 60 minute interval. There was much less background in the cardiac pool, which allowed for better delineation of the esophagus on the scintigram. Biopsy specimens taken just below the stricture revealed columnar epithelium with several areas in which parietal cells were present.

Case VI. A 69 year old white man had an 18 month history of heartburn. He noted retrosternal burning that seemed to reach his throat; it occurred after meals and seemed to be worse when lying down. He had no dysphagia, weight loss, or vomiting. The findings of the physical

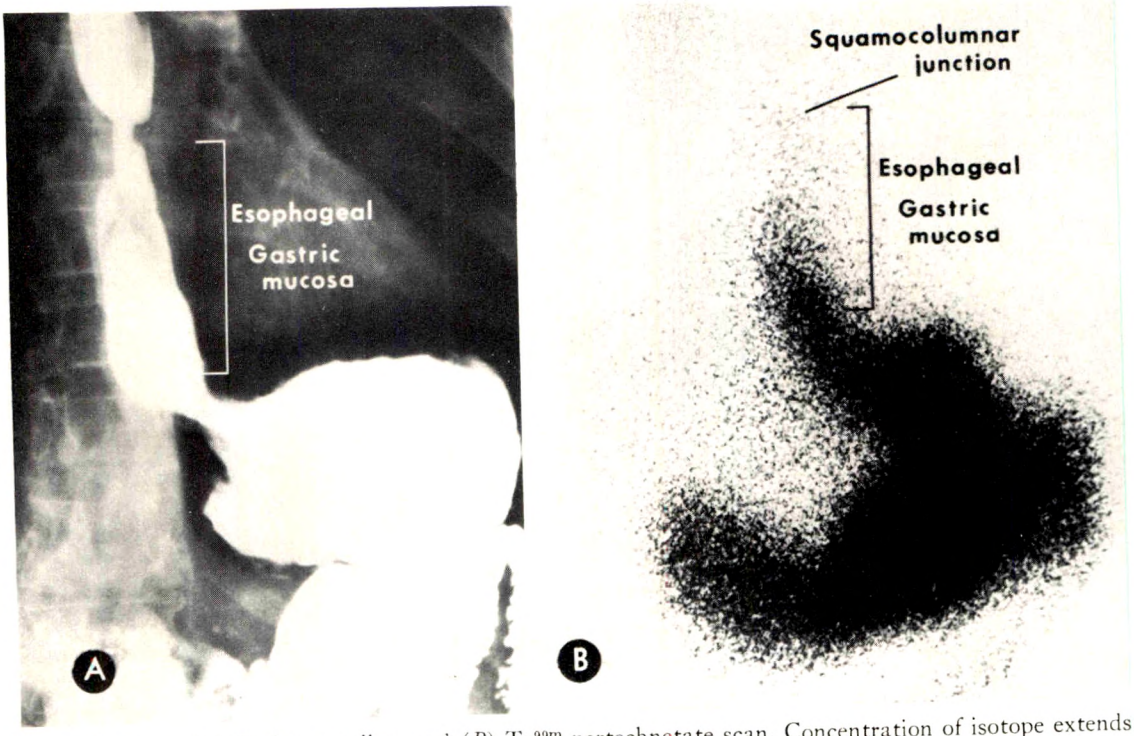

Fig. 5. Case III. (*A*) Barium swallow and (*B*) Tc^{99m} pertechnetate scan. Concentration of isotope extends above the esophagogastric junction to the level comparable to esophageal stricture on the roentgenogram. (Reproduced with permission from *Mayo Clin. Proc.*[4])

examination were normal. Fluoroscopy revealed a large esophageal hiatal hernia with ulceration at its superior margin and at least 2 additional ulcers in the esophagus just proximal to the level of the esophagogastric junction. The scintigram demonstrated concentration of Tc^{99m} pertechnetate by the stomach and the esophageal hiatal hernia; there was also an area of increased uptake in the region of the lower ulcer at the superior margin of the esophageal hiatal hernia and another superior to this, corresponding to the level of the ulcers in the esophagus (Fig. 9, *A* and *B*). Biopsy specimens demonstrated islands of gastric mucosa in the esophagus with inflamed, stratified, squamous epithelium surrounding these areas. This condition represents a variant of Barrett's esophagus and is termed Barrett's ulcer. It is characterized by one or more islands of the gastric mucosa in an esophagus with otherwise normal epithelium.

Comment. The usefulness of Tc^{99m} pertechnetate in the diagnosis of Barrett's esophagus is demonstrated by consideration of Cases I through VI. The technique may also be of value in excluding the diagnosis, when this cannot be done roentgenologically, as exemplified by Cases VII through IX.

Case VII. A 78 year old man presented with a

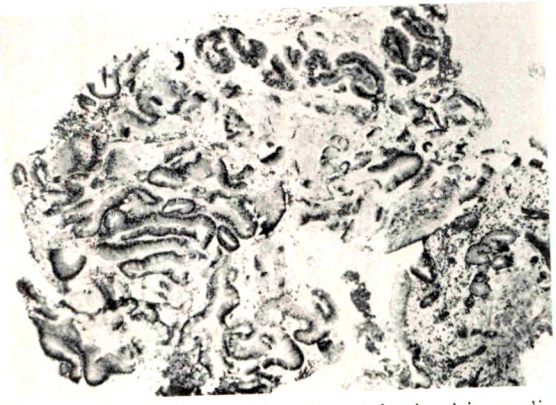

Fig. 6. Case III. Biopsy specimen obtained immediately below level of esophageal stricture, demonstrating gastric mucosa. (Hematoxylin and Eosin reduced from ×64.) (Reproduced with permission from *Mayo Clin. Proc.*[4])

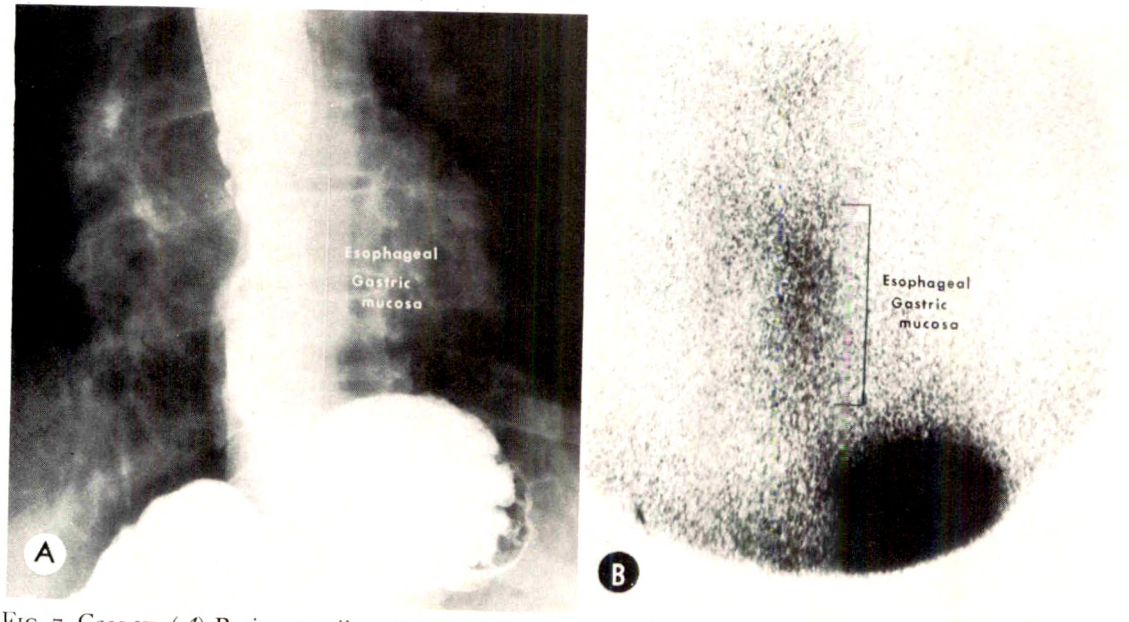

FIG. 7. Case IV. (*A*) Barium swallow and (*B*) Tc^{99m} pertechnetate scan. Isotope uptake is evident in esophagus to the level corresponding to stricture on the roentgenogram.

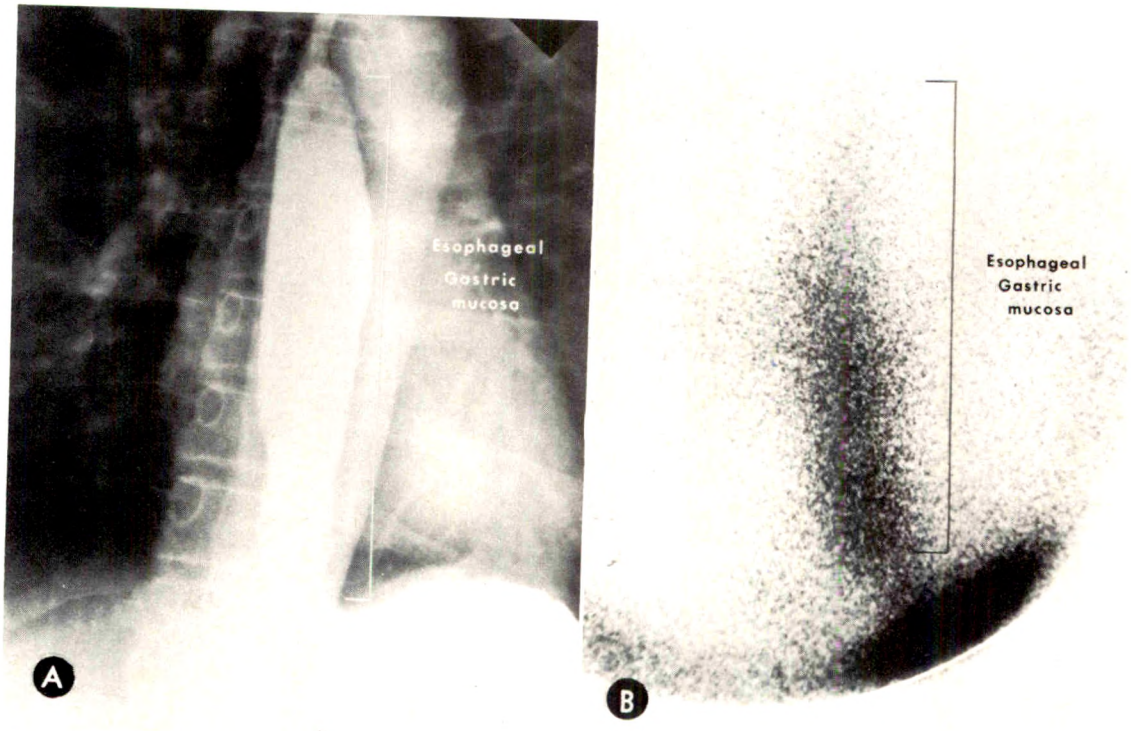

FIG. 8. Case V. (*A*) Barium swallow and (*B*) Tc^{99m} pertechnetate scan. Scintigram obtained 4 hours after injection reveals uptake of isotope in esophagus to level corresponding to stricture on the roentgenogram. Note essentially no background in cardiac pool.

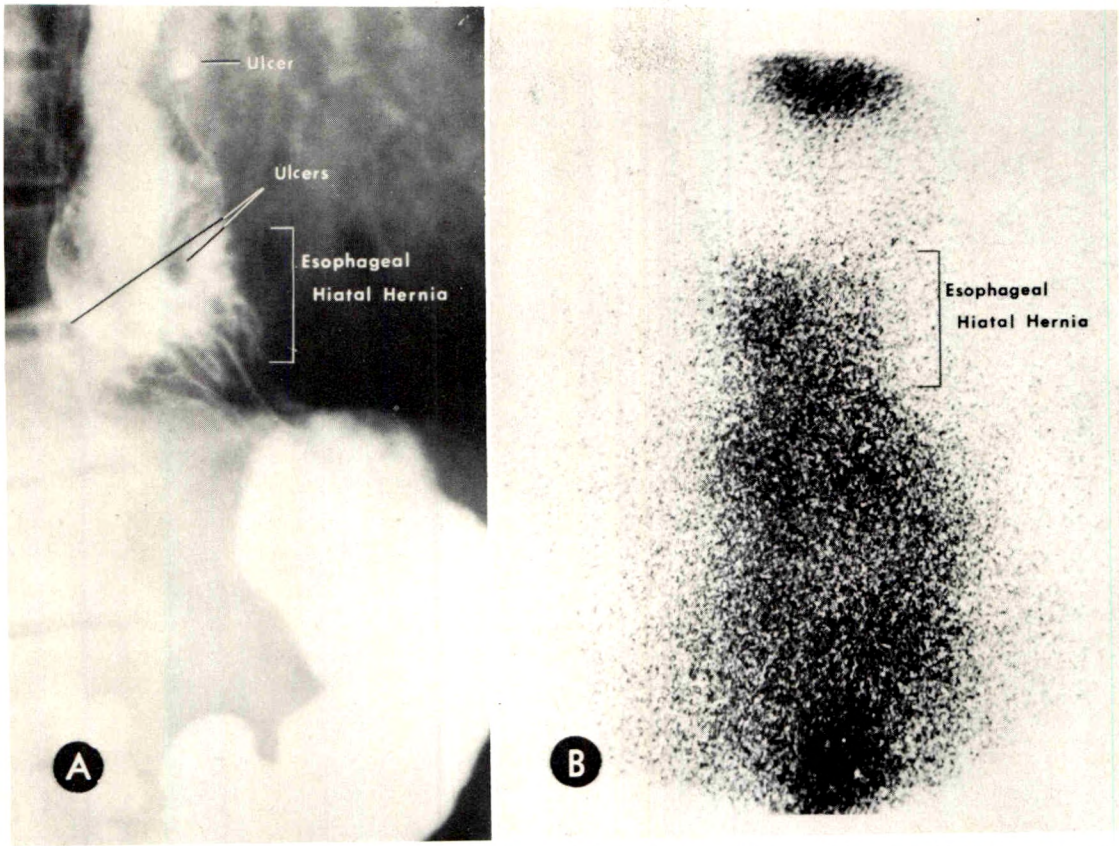

Fig. 9. Case VI. (*A*) Barium swallow and (*B*) Tc^{99m} pertechnetate scan. Uptake is increased in left upper portion of esophageal hiatal hernia (corresponds to lowest of ulcers on roentgenogram); uptake in esophagus corresponds to areas of ulceration above hiatal hernia on the roentgenogram.

4 year history of postprandial regurgitation, with an associated burning sensation in the anterior chest. The patient noted no nocturnal burning or regurgitation, no difficulty in swallowing, no weight loss, and no melena. A stricture of the mid-esophagus was demonstrated by fluoroscopy; no esophageal hiatal hernia was visualized and the roentgenographic esophagogastric junction was at the level of the hiatus. The significance and etiology of the stricture were not apparent roentgenographically. The scintigram demonstrated uptake of isotope by the stomach, but no activity in the esophagus (Fig. 10, *A* and *B*). With the aid of the scan, one could rule out the presence of Barrett's esophagus, which was not possible by means of the roentgenogram alone. Biopsy taken immediately below the level of the stricture confirmed the scan in excluding Barrett's esophagus by demonstrating inflamed, stratified, squamous epithelium, but no gastric mucosa.

Case VIII. A 72 year old man presented with a 10 year history of belching and bloating after meals with frequent regurgitation of gastric contents. During the past year he had lost 4.5 kg. (10 lb.). Fluoroscopy revealed a stricture of the mid-esophagus. The scintigram demonstrated uptake of isotope by the stomach, but no radioactivity in the lower esophagus (Fig. 11, *A* and *B*). Biopsy taken below the level of the stricture revealed inflamed, stratified, squamous epithelium, but no gastric mucosa.

Case IX. A 52 year old man had a history of anemia and weight loss. He had noted increasing fatigue for 1 year, but no melena, dysphagia, or heartburn. Fluoroscopy demonstrated a polypoid lesion of the lower esophagus; this was thought to be a carcinoma. The scintigram demonstrated concentration of the isotope in the stomach, but no uptake in the esophagus (Fig. 12, *A* and *B*). Biopsy specimens revealed adenocarcinoma of the stomach with extension

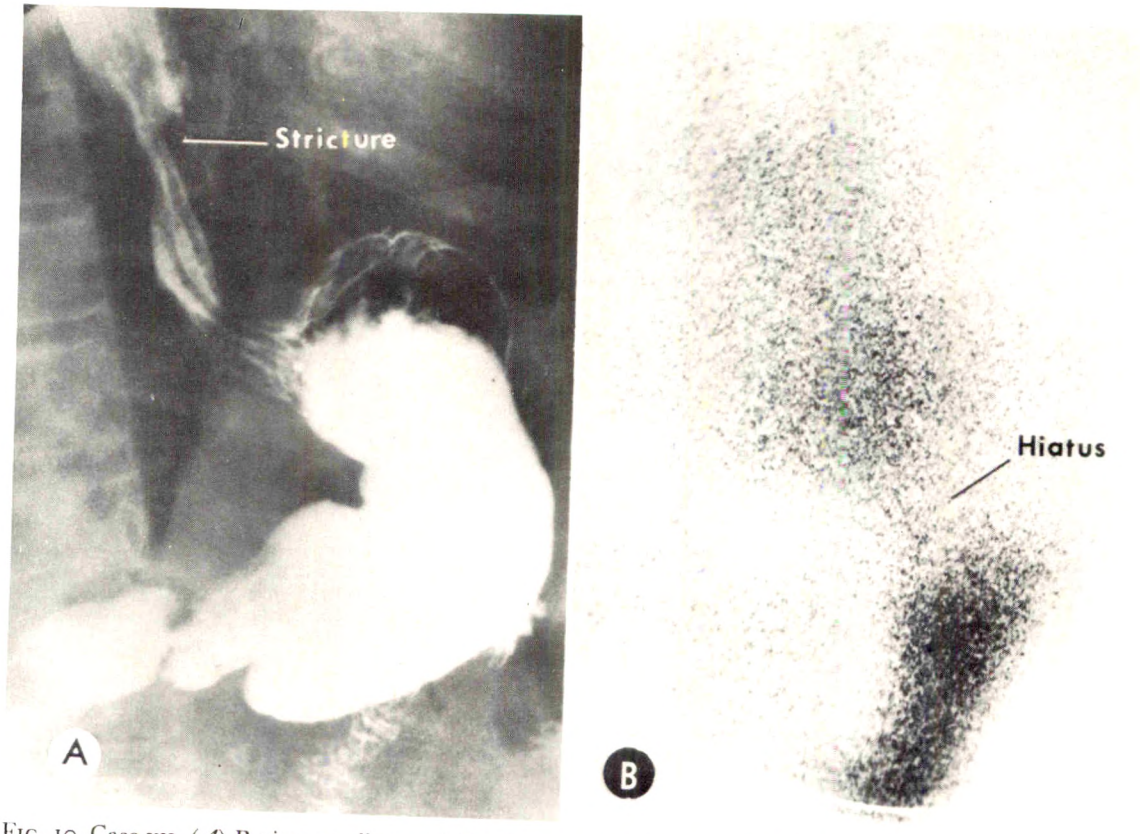

FIG. 10. Case VII. (*A*) Barium swallow and (*B*) Tc^{99m} pertechnetate scan. Uptake of isotope in the stomach, but no uptake of isotope above the esophagogastric junction at the level of hiatus.

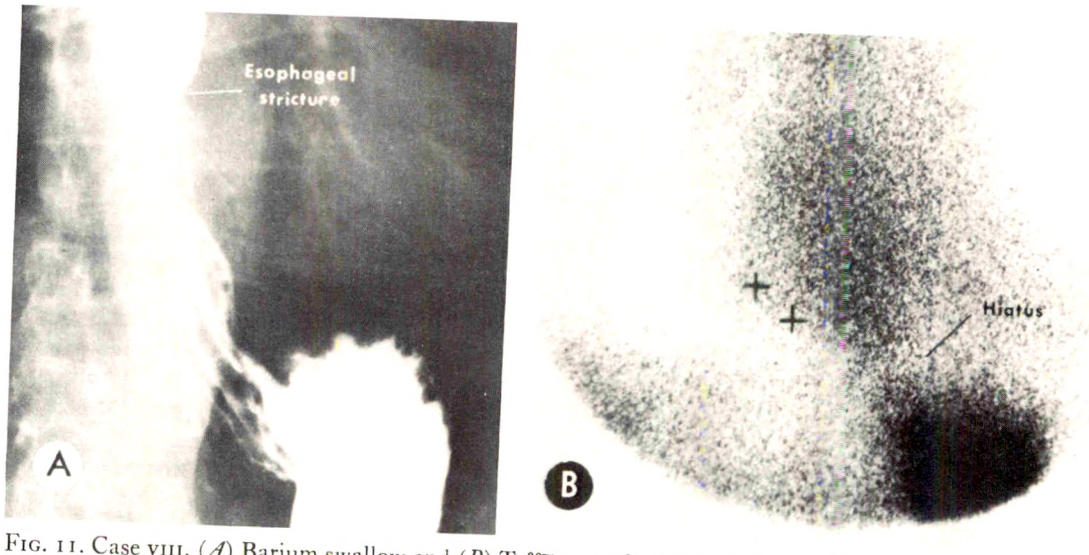

FIG. 11. Case VIII. (*A*) Barium swallow and (*B*) Tc^{99m} pertechnetate scintigram. There is uptake of isotope in the stomach (and some in the cardiac pool), but no uptake above the esophagogastric junction.

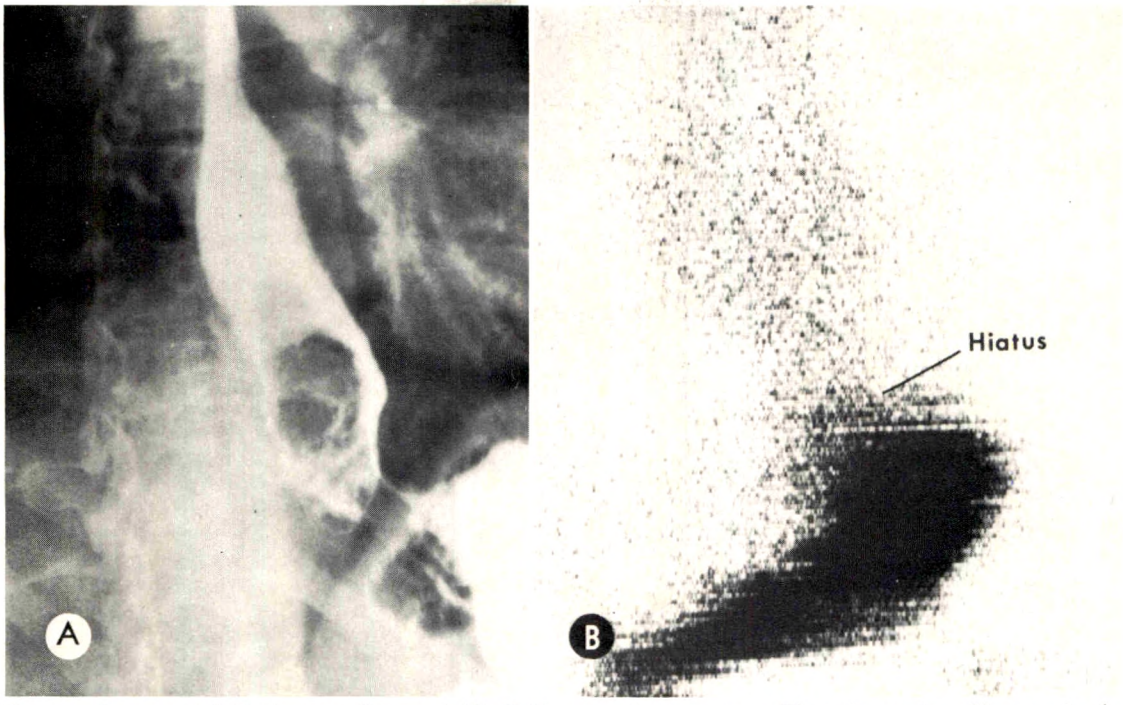

Fig. 12. Case IX. (*A*) Barium swallow and (*B*) Tc^{99m} pertechnetate scan. There is uptake of isotope in the stomach and less uptake in the neoplastic area of the stomach, but no uptake in the region of the tumor in the esophagus.

into the lower esophagus. Isotope was not taken up in the malignant gastric tissue and there were no roentgenographic features that would have been confused with Barrett's esophagus. An early, infiltrating carcinoma of the mid-esophagus, however, can resemble this entity roentgenographically and it is helpful to have scintigraphic evidence that malignant tissue does not concentrate Tc^{99m} pertechnetate.

DISCUSSION

To date, 9 patients have been studied with Tc^{99m} pertechnetate scintigraphy of the esophagus. In 5 patients, a diagnosis of Barrett's esophagus was made on the basis of abnormal uptake of Tc^{99m} pertechnetate by the lower esophagus, as seen on the scans. In each instance, the diagnosis was confirmed by tissue biopsy. In 1 additional patient who had the rare variant of Barrett's esophagus named Barrett's ulcer, the radioisotope was concentrated in the areas of esophageal ulceration; in this patient, too, diagnosis was confirmed by biopsy. Three patients with esophageal conditions other than Barrett's esophagus or Barrett's ulcer were also studied; scintigrams showed no esophageal uptake of pertechnetate, and biopsies confirmed absence of gastric mucosa in the esophagus of each patient.

In addition to our scintigraphic studies in these 9 patients, we have performed autoradiographs of the gastric mucosa in a group of dogs and rats in an attempt to localize the site of Tc^{99m} pertechnetate concentration. In our initial investigation, it was thought that autoradiographs of the gastric mucosa from 1 dog demonstrated uptake of Tc^{99m} pertechnetate in parietal cells.* Subsequently, numerous studies in dogs and rats revealed that the findings in our initial study were invalid. These later studies demonstrated intense uptake in the surface epithelial cells with essentially no activity observed in any other cell type. This finding is in conflict with the reports

* Oral presentation. American Roentgen Ray Society, Montreal, September, 1973.

of many authors who have stated that Tc^{99m} pertechnetate is probably concentrated and secreted by parietal cells.[3,4,7,10,11] None of these studies, however, included autoradiographic verification. Setälä and colleagues[13] were the first to state that Tc^{99m} pertechnetate was apparently concentrated in mucoid cells of the stomach in man, but they did not confirm this hypothesis by autoradiography. The finding that histologic localization is confined to the surface epithelial cell is fully consistent with the scintigraphic evidence for technetium uptake by gastric mucosa—both *in situ* and in extragastric locations—because this cell type is present in all types of gastric mucosa, irrespective of its anatomic location. A major objection to the proposal that concentration of this radionuclide is a property of parietal cells has been the frequent failure to histologically identify parietal cells in biopsies from patients in whom Barrett's esophagus had, in fact, accumulated Tc^{99m} pertechnetate as evidenced by scintigraphy. A review of the surgical specimens from our 6 histologically proven cases of Barrett's esophagus, in all of whom the scans were abnormal, revealed complete absence of parietal cells in all but one. By contrast, the gastric type of surface epithelial cells was present in every case. Thus, the finding of cellular uptake by gastric surface epithelial cells is fully in accord with the histopathologic and scintigraphic findings and offers a more satisfying explanation than could be obtained from parietal cell localization.

Carcinoma of the stomach has been studied with Tc^{99m} pertechnetate scintigraphy, and the uptake of Tc^{99m} pertechnetate is relatively low in neoplastic areas as compared with the surrounding normal gastric tissue.[11,13] In Case IX, there was a relatively decreased uptake of Tc^{99m} pertechnetate in the neoplastic region of the stomach and no uptake by the malignant gastric tissue that invaded the lower esophagus. Thus, uptake of Tc^{99m} pertechnetate in the esophagus appears to be a characteristic of benign ectopic gastric epithelium and one that is not observed after this tissue has undergone malignant transformation.

CONCLUSIONS

Scanning of the esophagus with Tc^{99m} pertechnetate for the diagnosis of Barrett's esophagus appears to be useful both in making the diagnosis and in helping to exclude it.

The technique offers a noninvasive approach to the identification of columnar epithelium lining the lower esophagus and promises to be useful in better understanding the etiology of the disorder.

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VALUE OF THE TILT UPSIDE-DOWN MANEUVER FOR ROENTGEN EXAMINATION OF PELVIC SMALL-BOWEL LOOPS*

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MILWAUKEE, WISCONSIN

EXPERIENCE gained with the clinical model of polyps in patients with Peutz-Jeghers syndrome indicates that discrete, polypoid small-bowel lesions, even when 3 to 4 cm. in size, frequently escape detection if the roentgen examination is limited to overhead projections or performed in a perfunctory manner.[2,3] When searching for localized small-bowel lesions, an essential feature in the roentgen examination is fluoroscopic inspection of each bowel loop accompanied by compression and appropriate spot filming. Application of this general principle, however, is commonly thwarted by ileal loops located within the bony pelvic cavity which are inaccessible for separation and compression by conventional techniques. In this circumstance, the ileal loops take on the appearance of an amorphous collection of barium, lacking in significant detail. Identification of a lesion lurking within the superimposed loops is unlikely. We have recently developed a simple upside-down maneuver which generally permits satisfactory evaluation of small-bowel loops located within the pelvic cavity.

METHOD

In our X-ray Department we routinely perform a small-bowel series using 20 to 24 oz. of a nonflocculating barium sulfate preparation. Posteroanterior roentgenograms, 14×17 inch, are obtained every 15 minutes for 1 hour and every 30 minutes thereafter until barium reaches the colon. Gastrografin (5 cc.) added to each 8 oz. cup of barium decreases transit time through

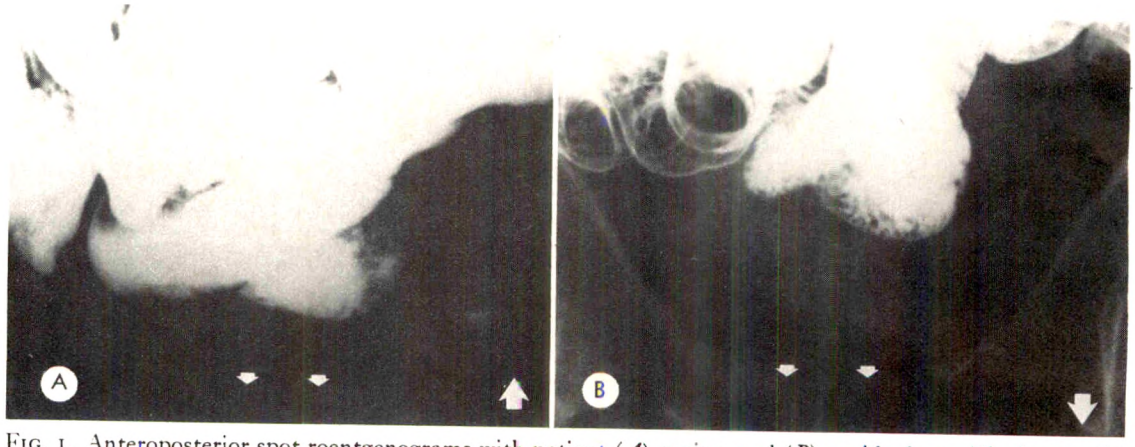

FIG. 1. Anteroposterior spot roentgenograms with patient (*A*) supine, and (*B*) upside-down. The large solid arrows point upward; the small solid arrows indicate the level of the pubic symphysis. On the conventional supine view, the small-bowel loops crowded within the bony pelvis appear as an amorphous barium density. With the subject upside-down, these loops slide partially out of the pelvis and are better seen. Gas often rises into the loops, providing a partial double-contrast examination. The confidence limit for judging these pelvic loops to be normal is much greater on the upside-down view than on the conventional supine view.

* From the Department of Radiology, the Medical College of Wisconsin, Milwaukee, Wisconsin.

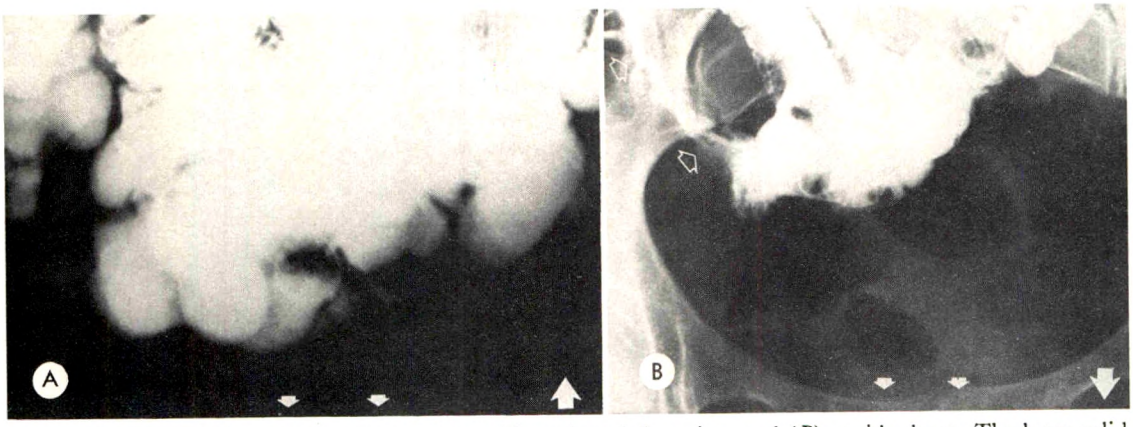

Fig. 2. Anteroposterior spot roentgenograms with patient (*A*) supine, and (*B*) upside-down. The large solid arrows point upward; the small solid arrows indicate the level of the pubic symphysis. Segmental involvement of the terminal ileum by Crohn's disease is not well shown on the conventional supine view. The upside-down view, however, clearly demonstrates the abnormal ileal segment (open arrows) revealing narrowing, wall thickening, and luminal contour irregularity. The remaining ileal loops show no morphologic abnormality.

the intestine, generally enabling completion of the examination in about 1 hour.[4] The large volume of barium fills long segments of the intestine in a continuous column. Consequently, the examiner can generally evaluate each small-bowel loop if fluoroscopy is performed immediately after gastroduodenal examination and at 30 and 60 minutes. Fluoroscopic examination of barium-filled ileal loops within the pelvis, however, is frequently inadequate, even when the bladder is distended with urine or when the subject is positioned prone over a pneumatic compression paddle. In this circumstance, the subject's shoulders are secured with either a harness or a brace, such as used for cervical myelography, and the roentgen table is tilted so as to bring the subject into a 40 to 80 degree head-down position. During this maneuver, small-bowel loops within the pelvis: (1) tend to fall out of the pelvic cavity into the abdomen; (2) generally become available for compression and palpation in their new position; and (3) often are filled by gas, resulting in double-contrast examination. This upside-down maneuver can be performed equally well with the patient prone or supine, but palpation is easier with the subject supine. The maneuver with accompanying fluoroscopy, compression and spot filming takes less than a minute to perform and is well tolerated by most subjects. Radiologists have used the upside-down position previously without untoward results to perform cervical myelography, promote gastroesophageal reflux and examine the gallbladder.[1] We have avoided using the maneuver in patients

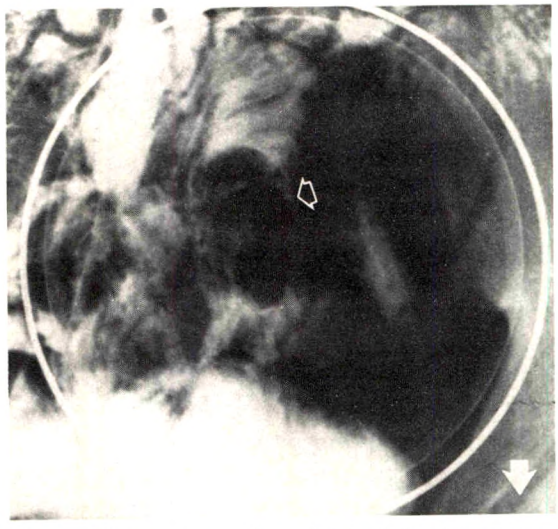

Fig. 3. Upside-down view obtained in the anteroposterior projection in a patient with Peutz-Jeghers syndrome. The solid arrow points upward. Pneumatic compression of an ileal loop which has partially slid out of the pelvis reveals a large polyp (open arrow). This lesion was not detected by conventional views.

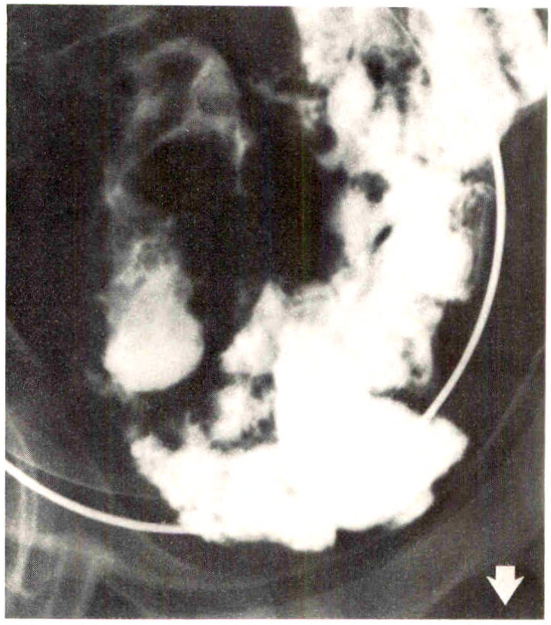

FIG. 4. Upside-down view, anteroposterior projection in a 12 year old boy with Crohn's disease. The solid arrow points upward. An abnormal loop featuring mucosal irregularity, nodularity and wall thickening is seen on the left side of the Figure (patient's right). The pelvic loops failed to slide upward, remaining adjacent to the pubic symphysis. This feature suggests fixation.

with known heart disease. high blood pressure, intracranial hypertension or glaucoma.

RESULTS

During the past year we have evaluated pelvic bowel loops using the upside-down maneuver in more than 50 patients undergoing a small-bowel series. In most of these examinations the method provided the radiologist with increased confidence that the distal bowel loops were normal (Fig. 1, *A* and *B*). In other examinations the method either showed localized ileal lesions to better advantage than conventional methods (Fig. 2, *A* and *B*) or revealed a lesion not shown on standard roentgenograms (Fig. 3). Failure of the pelvic intestinal loops to slide rostral several centimeters or more during the upside-down maneuver suggests fixation of the loops by adhesions, inflammatory tissue or neoplasm (Fig. 4). This hypothesis is supported by the observation that all 7 patients in our series who demonstrated pelvic fixation of small-bowel loops had disorders consistent with this observation. Of these 7 patients, 3 had Crohn's disease, 2 postoperative adhesions, 1 pelvic neoplasm and 1 radiation enteritis. Further evidence supporting this observation, however, is needed.

SUMMARY

The upside-down maneuver is a useful ancillary technique for examining pelvic small-bowel loops which are not satisfactorily examined by conventional methods. The maneuver is readily performed by the radiologist and tolerated by most patients without untoward effects.

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HEPATIC LYMPHATICS DEMONSTRATED BY PERCUTANEOUS TRANSHEPATIC CHOLANGIOGRAPHY*

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INTRAHEPATIC and extrahepatic lymphatic vessels were demonstrated by the intraparenchymal injection of contrast material into the liver during percutaneous transhepatic cholangiography in patients with liver disease. Six cases are presented to draw attention to this unusual occurrence and to aid the roentgenologist in identifying hepatic lymphatics.

Moreno and colleagues[6] were first to describe hepatic lymphatic opacification after the intraparenchymal injection of sodium diatrizoate during percutaneous transhepatic cholangiography. Their observation was made in patients with alcoholic cirrhosis accompanied by abdominal ascites; filling of lymphatics was not noted in cirrhotic patients without ascites. Since their study in 1963, hepatic lymphatics have been demonstrated during percutaneous transhepatic cholangiography in only 9 other reported cases.[2,7] It is not clear in these last 9 cases if ascites was present.

CLINICAL AND ROENTGENOGRAPHIC FINDINGS

The age of the patients in our series and the type of liver disease varied. One patient had chronic, active hepatitis: the other 5 had some form of nonalcoholic biliary cirrhosis (Table 1). Two of these 5 patients (Cases III and IV) had primary biliary cirrhosis, while the other 3 had cholestasis with cirrhosis secondary to obstruction.

TABLE I

SUMMARY OF FINDINGS

	Case					
	I	II	III	IV	V	VI
Age, sex	54 yr., F	6 mo., F	44 yr., F	48 yr., F	61 yr., M	81 yr., M
Ascites	o	+	o	o	o	o
Esophageal varices	o	o	o	o	o	o
Total serum bilirubin (mg./100 ml.)	11.0	9.4	8.2	10.0	19.5	15.0
Dilated bile ducts on percutaneous cholangiogram	+	o	o	o	+	o
Diagnosis by liver biopsy	Secondary biliary cirrhosis with chronic pericholangitis	Secondary biliary cirrhosis due to biliary atresia	Primary biliary cirrhosis with portal scarring, diffuse lymphocyte infiltrate, and proliferation of small bile ducts	Primary biliary cirrhosis	Nonspecific obstructive cholestasis with bile lakes; secondary biliary cirrhosis	Chronic, active hepatitis
Clinical diagnosis	Recurrent cholangitis due to common bile duct stricture resulting from surgical exploration during cholecystectomy	Biliary atresia with *Klebsiella* and *Pseudomonas* septicemia	Sclerosing cholangitis and chronic ulcerative colitis	Idiopathic jaundice; previous liver biopsy specimen showing biliary cirrhosis	Carcinoma of head of pancreas with obstructive jaundice	Hepatitis

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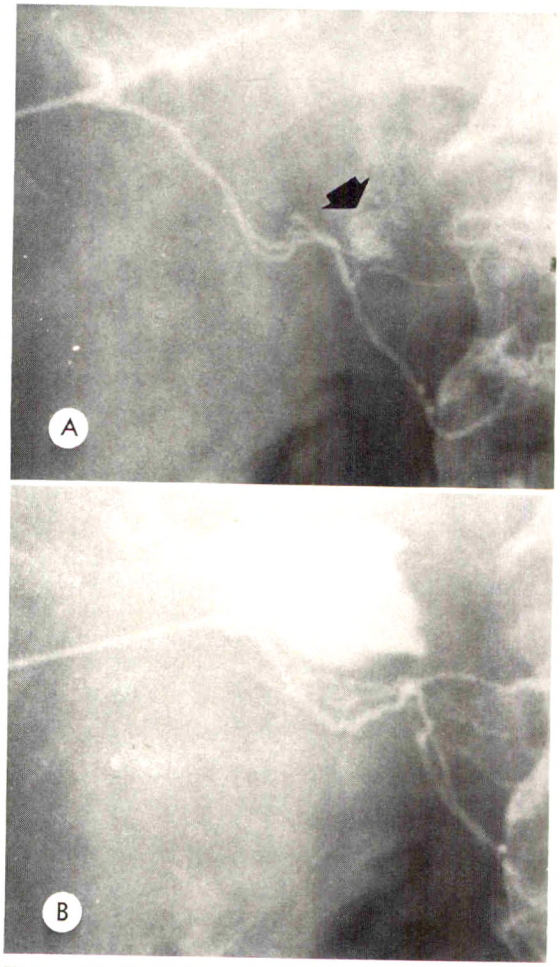

FIG. 1. Case VI. Intraparenchymal injection of contrast material resulted in opacification of a deep lymphatic channel. (*A*) The lymphatic channel divides into 2 branches in the region of the gastrohepatic ligament and courses medially to the region of L_1. A lymph node is faintly opacified (arrow) by a small lymphatic branch. (*B*) Further intraparenchymal injection led to opacification of several lymphatic branches coursing horizontally to the region of the L_1 vertebral body.

Only 1 patient (Case II), a 6 month old infant, had abdominal ascites.

In each case, intraparenchymal injections of sodium diatrizoate (50 per cent) were made during percutaneous transhepatic cholangiography. The injections resulted in demonstration of irregular channels that filled from the site of injection towards the hilus of the liver, generally in the same orientation as the intrahepatic bile ducts (Fig. 1, *A* and *B*). However, these vessels varied in appearance from the bile ducts in that they were irregular and beaded; some appeared to have valves (Fig. 2). The lymphatic channels extended beyond the hilus towards the area overlying the spine in the region of T_{12}, along the gastrohepatic ligament (Fig. 3; 4; and 5). In some instances, the lymphatic channels were arranged perpendicular to the biliary ducts. Because the contrast material was water-soluble, no residual contrast material was noted in lymph nodes on the day after each study.

The filling of lymphatic vessels and the persistence of contrast material in these channels over several minutes were in contradistinction to the rapid outflow of contrast material injected into hepatic veins. Hepatic venous channels were oriented in a direction toward the heart, and remained opacified only a few seconds. In 5 cases, contrast material was also injected into the biliary tree and the biliary channels were seen to opacify. In Case VI, the biliary tree was not opacified. Of interest was that in

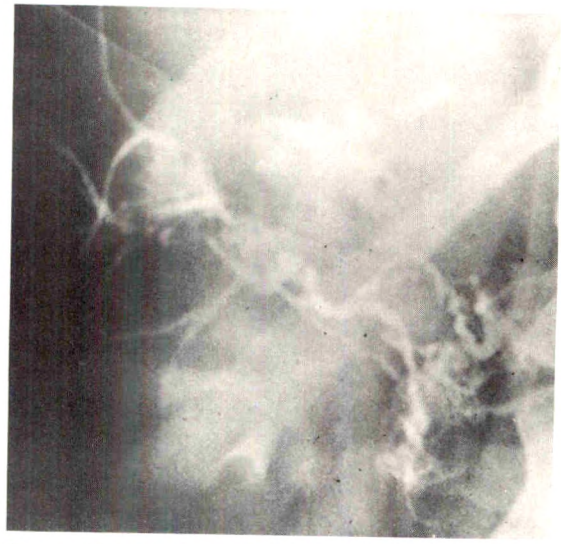

FIG. 2. Case IV. In the right posterior oblique projection, irregular, serpiginous lymphatic vessels, some beaded in appearance, may be seen converging in the region of the celiac lymphatics.

only 2 patients (Cases I and V) were the biliary ducts actually seen to be dilated.

DISCUSSION

The hepatic lymphatic opacification during percutaneous transhepatic cholangiography was a fortuitous occurrence. Moreno *et al.*,[6] in noting the lymphatic filling from parenchymal hepatic injection, described the beaded irregular appearance that we saw in our cases; but all of their patients with hepatic lymphatic opacification had ascites. Also, the opacified lymphatics rapidly emptied in their patients, as opposed to ours, in whom the contrast material remained in the lymphatic vessels for several minutes. Moreno *et al.*[6] postulated that dilated lymphatics, which carry increased flow in patients with cirrhosis and ascites, permit enough contrast medium to be removed from the extravascular parenchymal spaces of the liver to allow roentgenographic opacification. This explanation found basis because all of their patients had ascites. Ascites was present in only 1 of our patients, a 6 month old infant with biliary cirrhosis and septicemia secondary to biliary atresia. Lymphatics were opacified in our other 5 patients who had no ascites. Moreno *et al.*[6] also mentioned that they were not able to demonstrate lymphatics in normal dogs, but, when hepatic inflammation was produced experimentally, lymphatic flow was seen to increase. Liver biopsy specimens from our patients showed active inflammation in 1 patient with biliary cirrhosis secondary to biliary atresia (Case II). The chronic, active hepatitis present in Case VI is the only example of primary inflammatory liver disease.

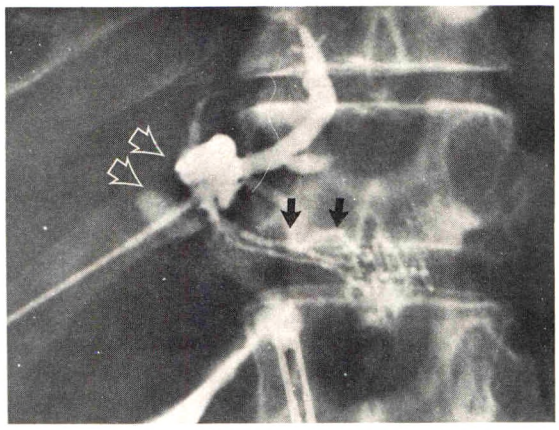

FIG. 4. Case V. Lymphatic channels fill from an intraparenchymal collection (open white arrows) of contrast material and extend beyond the margin of the liver to the area overlying the T_{12}-L_1 interspace (black arrows). A branch of the left biliary duct system has filled.

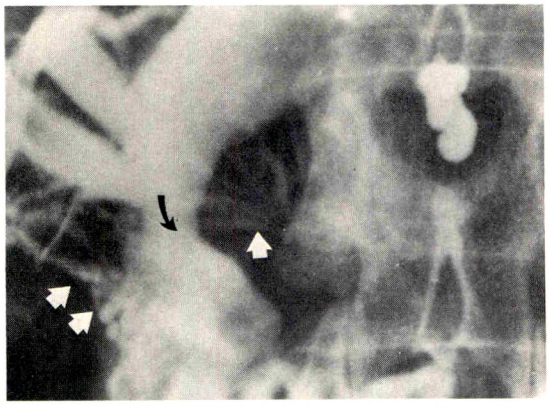

FIG. 3. Case I. The right and left hepatic bile ducts are opacified as is the choledochojejunostomy (black arrow). Hepatic lymphatics (white arrows) are also opacified.

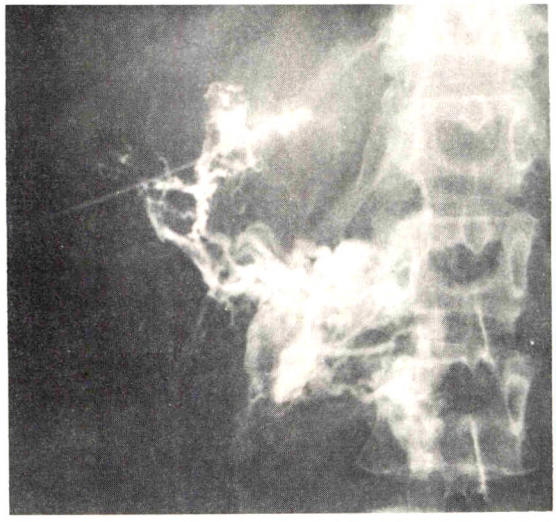

FIG. 5. Case III. Irregular, beaded, serpentine, lymphatic vessels in great numbers crowd the region of the porta hepatis and celiac lymph nodes in a patient with sclerosing cholangitis.

The major features that distinguish lymphatic channels from irregular biliary ducts are the undulating pattern of dilatation, which produces a beaded appearance (Fig. 5), and the presence of fine, lucent bands caused by valves. Lymphatic channels follow a serpiginous course in contrast to biliary ducts. In addition, the lymphatic vessels extend well beyond the region of the liver hilus into the gastrohepatic ligaments. They do not parallel the course of the common bile duct but extend horizontally towards the level of the T_{12} vertebral body. The appearance and distribution of hepatic drainage have been verified by lymphangiography.[5]

There are 2 lymphatic systems in the liver: a superficial system beneath the capsule which is connected by lymphatic channels to a deep lymphatic system which courses with the portal channels. The deep lymphatic plexuses follow the portal vein, bile duct, and hepatic artery to the edge of each lobule of the liver. The 2 systems join together as larger collecting vessels that leave the liver at the hilus. These vessels enter lymph nodes in the region of the hilus and gastrohepatic ligament where they are joined by lymphatics from the extrahepatic biliary tract. These larger channels, in turn, course horizontally towards the celiac lymph nodes and, from there, empty into the cisterna chyli. Some deep lymphatics follow hepatic veins to the inferior vena cava as it passes through the diaphragm.

One conspicuous feature of normal hepatic lymphatics is the presence of valves in the larger collecting vessels and main lymphatic channels. No valves are apparent in the lymphatic capillary vessels.[8]

The occurrence of increased hepatic lymph flow in patients with cirrhosis and ascites is a well-known phenomenon.[1,4,6] Distended hilar lymphatics have also been seen, however, in cases of extrahepatic biliary obstruction.[3] Extrahepatic biliary obstruction, due to carcinoma of the head of the pancreas, was associated with dilated hepatic lymphatics in Case v (Fig. 4). In primary biliary cirrhosis or primary intrahepatic cholestasis, large lymphatics and hilar lymph nodes have been noted (Cases III and IV).[3]

Percutaneous transhepatic cholangiography is not performed specifically to demonstrate hepatic lymphatics; it is important, however, to recognize the characteristic roentgenographic features of hepatic lymphatics so that they may be differentiated from biliary ducts and hepatic vascular channels.

SUMMARY

Intrahepatic and extrahepatic lymphatic vessels were opacified by the intraparenchymal injection of contrast material during percutaneous transhepatic cholangiography in 5 patients with cirrhosis and 1 patient with chronic, active hepatitis. The lymphatic channels had a beaded, irregular appearance. They converged in the region of the liver hilus and extended outside the boundaries of the liver to the region of the T_{12} vertebral body.

The location and the roentgenographic appearance of these lymphatic channels should distinguish them from biliary ducts and hepatic vessels.

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THE SPHEROID SIGN*

A NEW SIGN FOR ACCURATE DIFFERENTIATION OF INTRAMURAL FROM EXTRAMURAL MASSES

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THE chief responsibility of the roentgenologist in describing neoplasms is for their detection and the determination of their exact location. However, the specific histologic type is usually not apparent and the site of origin often cannot be identified. The vector principle, explained by Whalen *et al.*[2] in the differential diagnosis of abdominal masses, aids the roentgenologist in locating lesions by noting the effect that the involved organ may exert on adjacent structures. It does not, however, relate to differentiating intramural from extramural lesions affecting the gastrointestinal tract.

The form taken by any neoplasm in the gastrointestinal tract is dependent on: (1) its degree of invasiveness; (2) its consistency; and (3) its site of origin. The present study deals with the site of origin.

There is evidence that neoplasms begin either as single cells or as fields of closely knit cells that become aberrant.[1] General roentgenologic experience shows that, in retrospect, the large lesions appear to have originated from much smaller foci. These lesions slowly expand centrifugally, compressing and distorting surrounding normal tissues. The same principle of growth and expansion also holds for cystic masses. In addition, most cancers grow in a more or less predictable manner, varying only according to the individual type of cancer.

We postulated that by determining where the center of the mass lies in relation to the projected luminal contour of the bowel, the roentgenologist can predict with high accuracy whether the mass is intramural (mucosal or submucosal) or extramural. We tested the validity of this "spheroid" sign in 103 roentgenograms that showed a mass causing a barium defect.

MATERIAL AND METHODS

The cases were accumulated from the files of the 2 teaching hospitals of the University of California, San Francisco. Only those roentgenograms showing the lesions in complete or partial profile against the

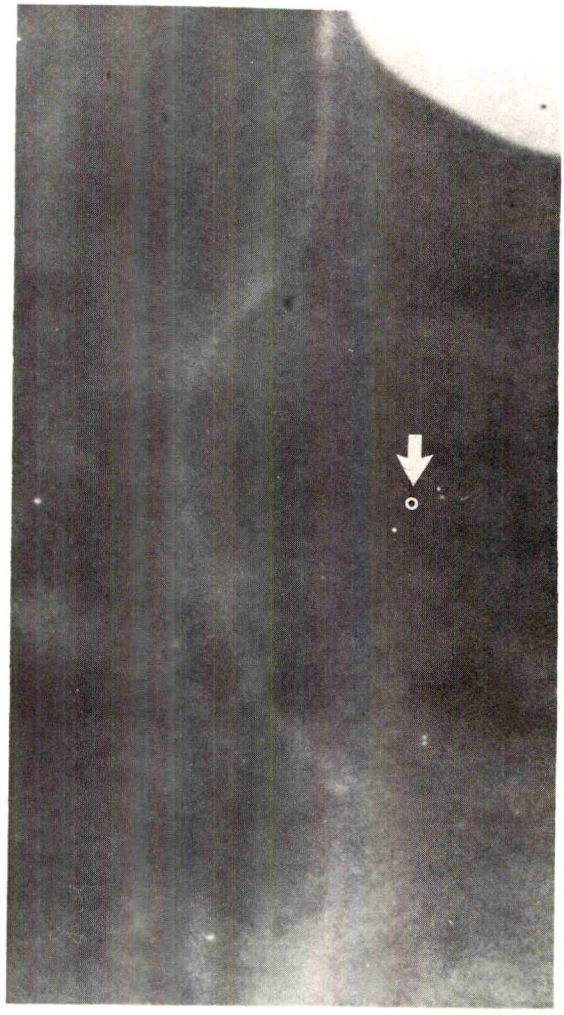

FIG. 1. Carcinoma of the cervix. Air-contrast study of rectum shows defect with center (→○) lying outside projected rectal contour.

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luminal contour of the viscus were included in the study. In all instances pathological proof of the site of the lesion was available.

The method devised assumed 5 sets of roentgenologic principles based on the location of the center of the mass.

(1) Masses with estimated centers lying outside the projected luminal contour are extramural (Fig. 1).

(2) Masses with estimated centers lying within the projected luminal contour are intramural (whether mucosal or submucosal) (Fig. 2, *A–E*).

(3) Masses with estimated centers lying along the projected luminal contour are also intramural (whether mucosal or submucosal) (Fig. 3).

(4) Oval, rather than round masses, with the estimated centers outside, or inside or along the projected contour of the lumen are extramural, or intramural respectively (Fig. 4).

(5) Masses cannot always be viewed in profile. The slight obliquity of a mass seen partially face-on (Fig. 5, *A–C*) results in the appearance of 2 luminal defects of different size. If the estimated center of either of these 2 falls outside the projected contour of the lumen, the lesion is extrinsic. If the estimated centers of both fall within the projected luminal contour, the lesion must necessarily be intramural.

Three roentgenologists, of varying experience and not familiar with the cases, tested the method. Roentgenologist A, experienced in gastroenterology, helped develop the method of the spheroid sign and was instructed to determine the site of origin depending upon whether the center of the mass lies within or outside the projected luminal contour of the barium-containing viscus. Roentgenologist B, who had just finished his residency in diagnostic radiology and obtained board certification, had no prior knowledge of the spheroid sign. He was tested before and then after an explanation of the principles of the sign. Roentgenologist C, a first-year resident in diagnostic radiology, was explained the sign before attempting to determine the site of origin of the 103 masses.

Only that portion of the roentgenogram which showed the barium defect in complete or partial profile was shown for viewing (Fig. 6, *A* and *B*). This eliminated criteria other than the spheroid sign from entering into the diagnosis.

RESULTS

Results of the testing are presented in Table 1. Roentgenologist A correctly predicted the site of origin in 43 of 45 extramural masses. The 2 errors were in defects caused by pancreatic pseudocysts (Fig. 7, *A* and *B*). He was correct, however, in predicting the site of origin of 5 other pseudocysts. He correctly predicted the site of origin in 58 of 58 intramural masses. His over-all accuracy was 98.1 per cent.

Without knowledge of the principles of the spheroid sign, Roentgenologist B correctly determined the site of 36 of 45 extramural masses, and 44 of 58 intramural masses—an accuracy of 77.7 per cent. After explanation of the spheroid sign, by determining the origin of 4 more intramural and 3 more extramural masses, his accuracy increased to 84.5 per cent.

By using the spheroid sign only, Roentgenologist C was correct in detecting the site of 53 of 58 intramural and 27 of 36 extramural masses. This represents 77.7 per cent accuracy.

DISCUSSION

The roentgenologist needs to distinguish intramural from extramural masses in making a differential diagnosis because the layer of origin is probably one of the most important factors in determining the gross form taken by neoplasms. With the spheroid sign the roentgenologist can, with high accuracy, predict whether a mass that produces a defect in a barium column originates intramurally (mucosal or submucosal) or extramurally. Sophisticated techniques have made the mucosal surfaces of the esophagus, stomach and duodenum, as well

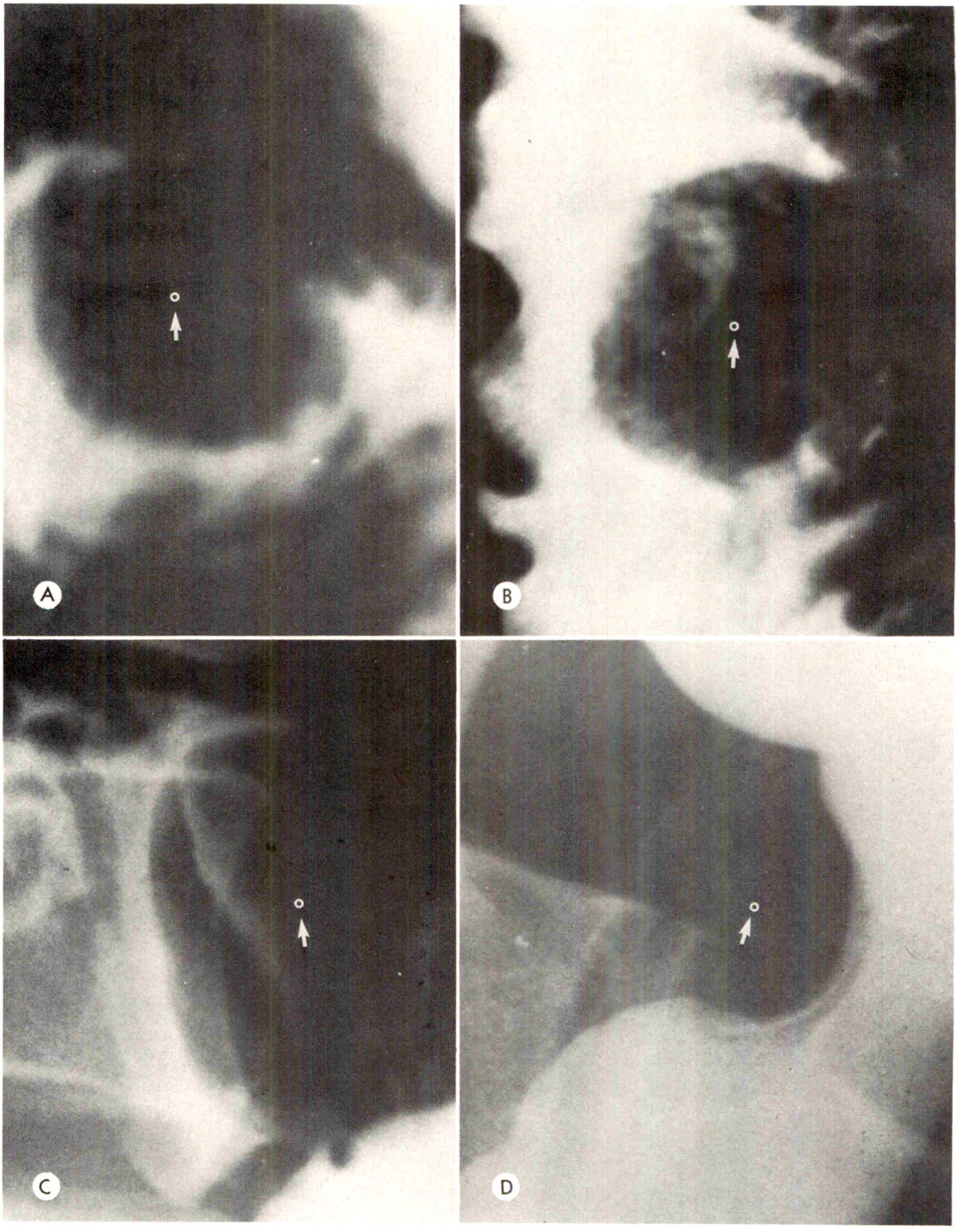

FIG. 2. Masses with centers (→○) lying within luminal contour of bowel. (*A*) Carcinoid. (*B*) Pancreatic rest. (*C*) Duodenal fibroma. (*D*) Adenomatous polyp.

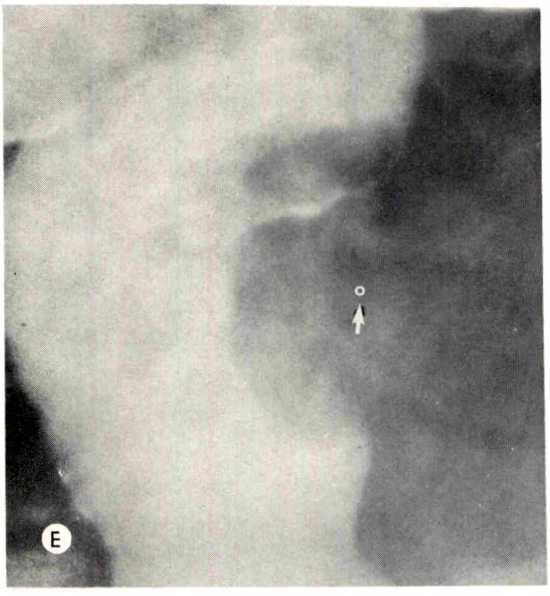

Fig. 2. (*E*) Adenocarcinoma.

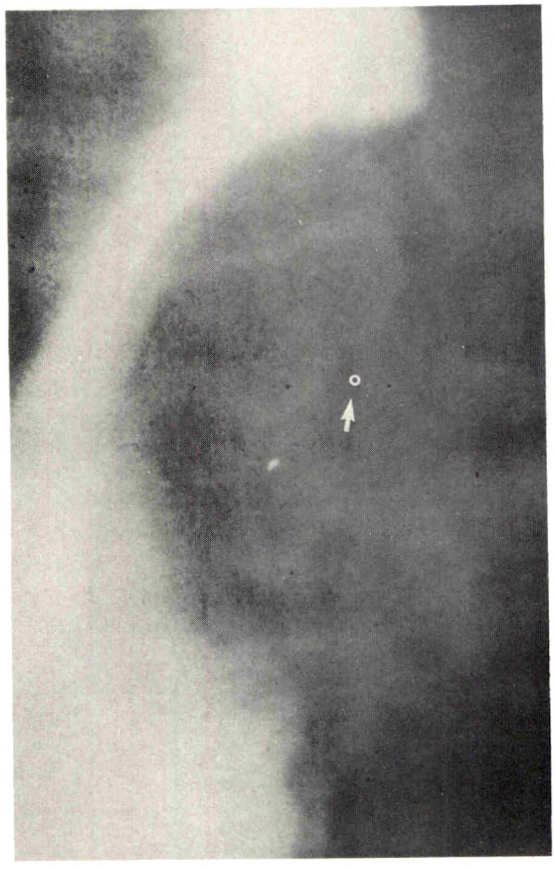

Fig. 3. Esophageal schwannoma. Center of mass (→○) is on projected contour of bowel.

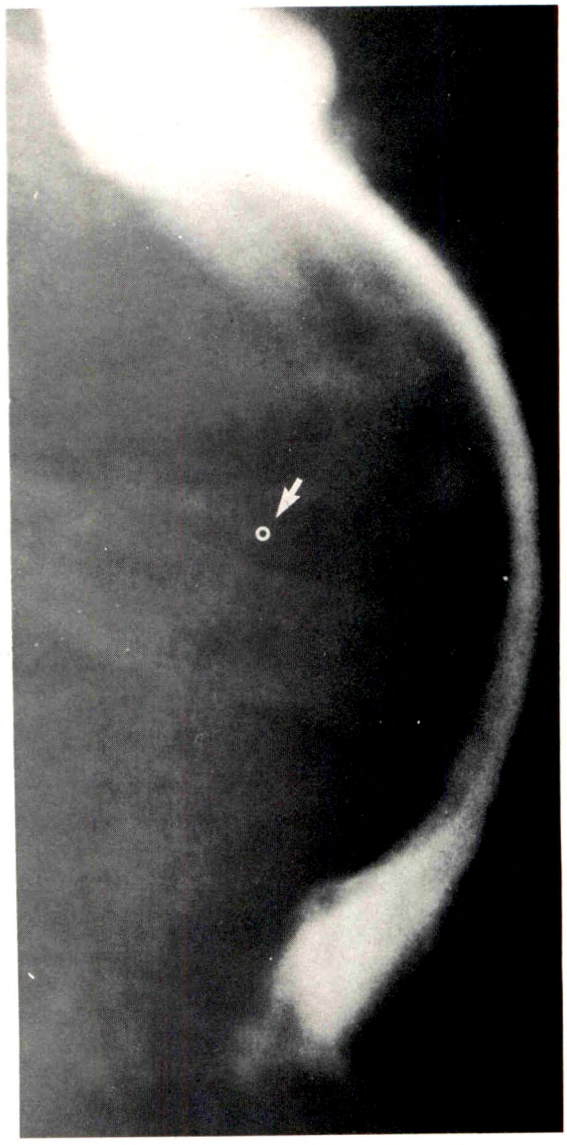

Fig. 4. Duplication cyst. An oval defect is seen with center (→○) on projected luminal contour.

as the entire colon, readily visible to the endoscopist. The cooperative efforts, therefore, of the endoscopist and the roentgenologist can often lead to the correct determination of mucosal, submucosal, and extramural masses affecting the gastrointestinal tract. The roentgenographic signs differentiating mucosal from submucosal masses are presently being studied in this department.

Interestingly, Roentgenologist A made

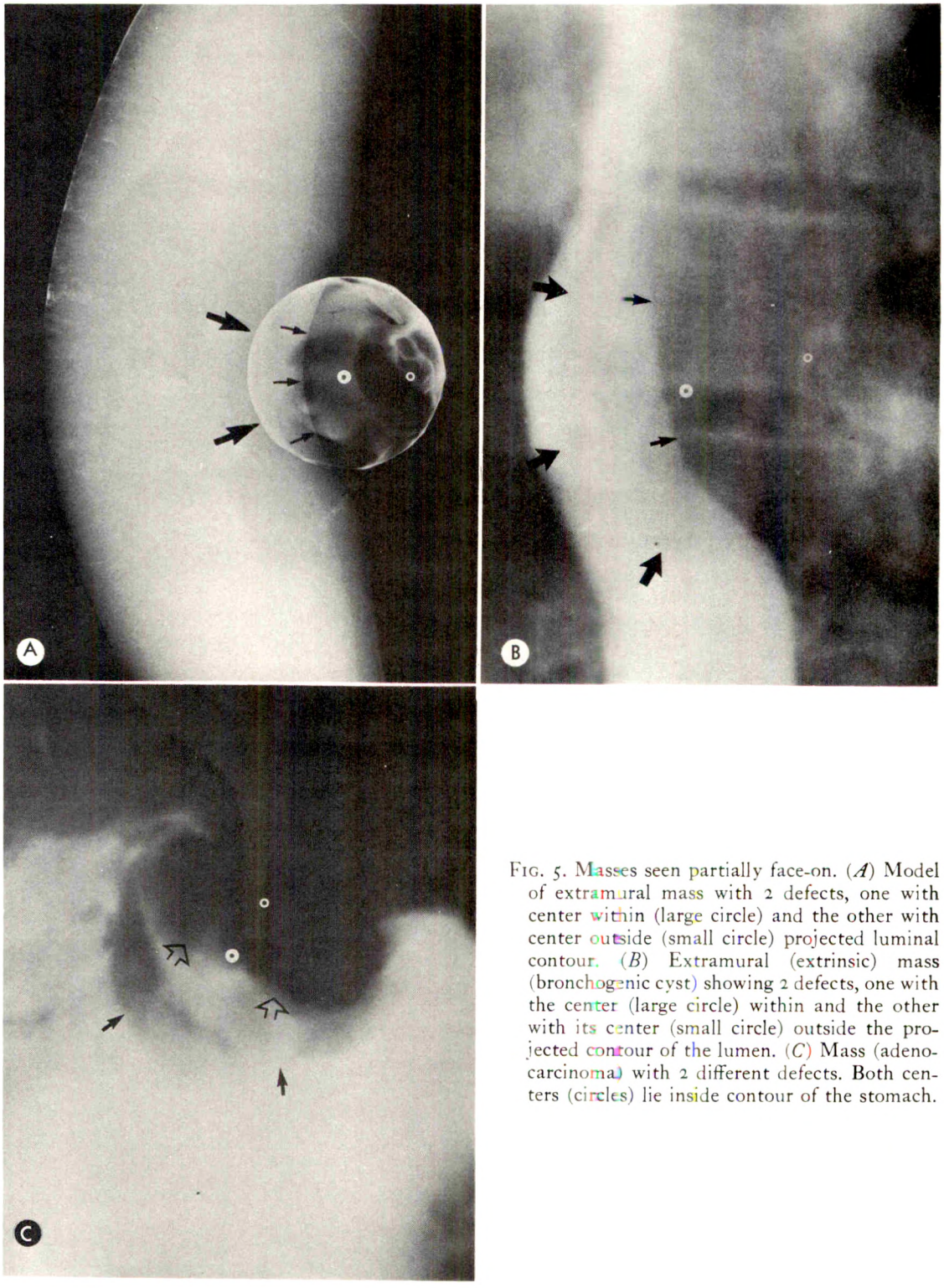

FIG. 5. Masses seen partially face-on. (*A*) Model of extramural mass with 2 defects, one with center within (large circle) and the other with center outside (small circle) projected luminal contour. (*B*) Extramural (extrinsic) mass (bronchogenic cyst) showing 2 defects, one with the center (large circle) within and the other with its center (small circle) outside the projected contour of the lumen. (*C*) Mass (adenocarcinoma) with 2 different defects. Both centers (circles) lie inside contour of the stomach.

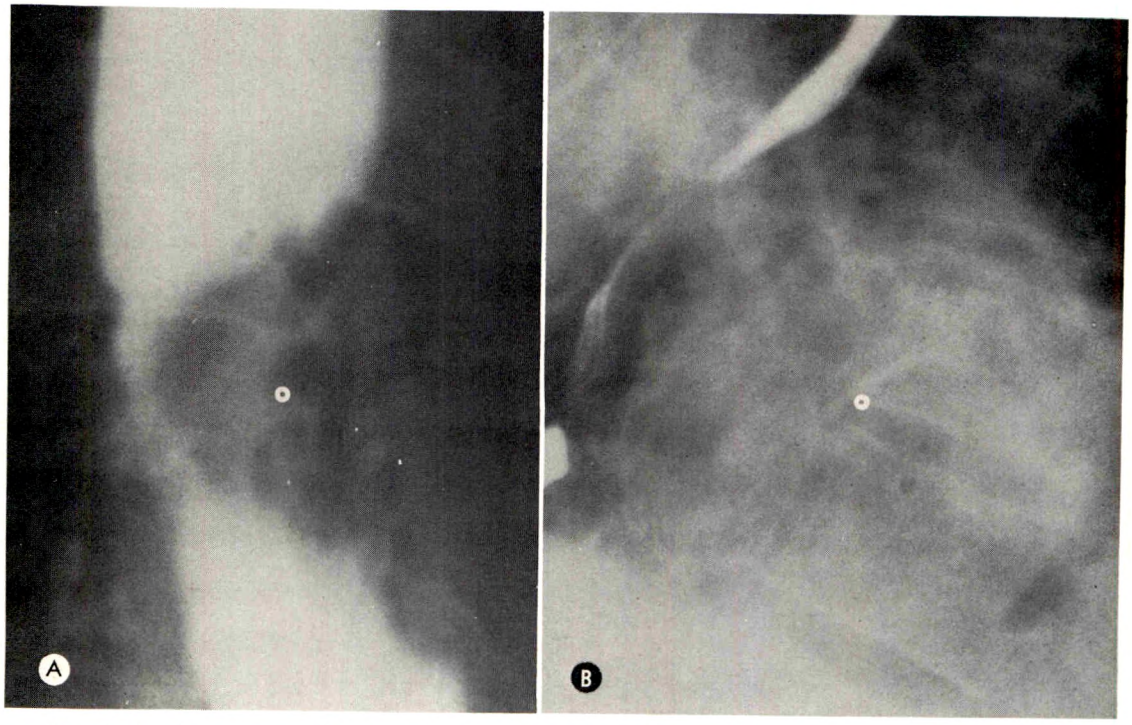

Fig. 6. Aortic aneurysm. (*A*) Face-on view of the mass showing center (circle) within the luminal contour but which is clearly extramural when viewed in profile (*B*).

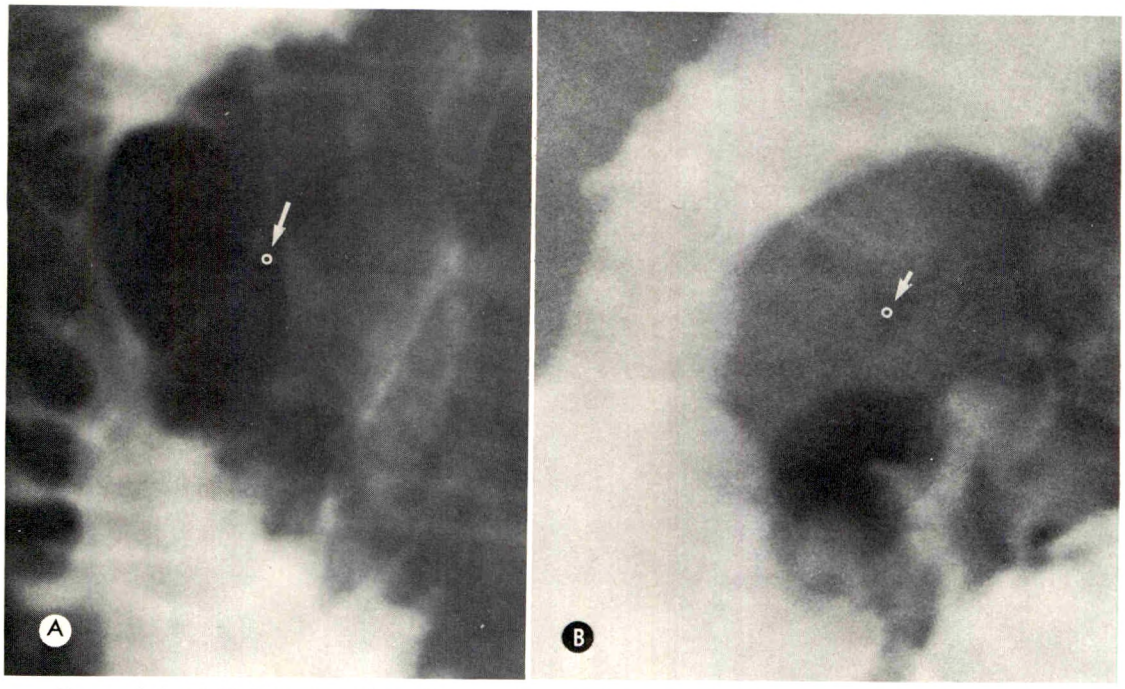

Fig. 7. (*A* and *B*) Two examples of pancreatic pseudocyst, both with centers within the luminal contour of the duodenum, both erroneously interpreted as intramural masses.

TABLE I

RELIABILITY OF THE SPHEROID SIGN IN DIFFERENTIATING INTRAMURAL FROM EXTRAMURAL MASSES

Mass	Roentgenologist			
	A	B Trial		C
		I*	II	
Intramural (58)	58	44	48	53
Mucosal (34)				
Submucosal (24)				
Extramural (45)	43	36	39	27
Total	101	80	87	80
Per cent accuracy	98.1	77.7	84.5	77.7

* Before knowledge of the spheroid sign.

only 2 errors in the 103 cases. Both concerned pancreatic pseudocysts that were incorrectly diagnosed as intramural masses. Even in retrospect these 2 defects appear to have estimated centers lying within the luminal contour of the bowel. We believe this finding can be explained. Pancreatic pseudocysts liberate proteolytic enzymes which, in themselves, may cause edema and thickening of bowel wall and mucosa. This thickening may give the spurious appearance of an intramural lesion, rather than the appearance of the predominantly extramural pseudocyst. Roentgenologist A did, however, correctly locate 5 other pseudocysts.

SUMMARY

Barium-column defects with estimated centers lying within or outside the projected luminal contour of the bowel are likely to be intramural or extramural masses, respectively. Those with centers lying along the luminal contour are likely to be intramural. When a mass is viewed partially face-on, 2 defects in the barium column appear. If either of these has an estimated center lying outside the luminal contour of the bowel, the origin of the mass is extramural. If both estimated centers lie within the projected luminal contour, the mass arises intramurally. This "spheroid" sign was tested in a blind study and found to be highly reliable.

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Vol. 123, No. 2

MICROANGIOGRAPHY OF THE WHITE PULP OF THE SPLEEN*

By ALAIN E. DUBREUIL, M.D., PETER G. HERMAN, M.D., NICHOLAS L. TILNEY, M.D. *and* HARRY Z. MELLINS, M.D.
BOSTON, MASSACHUSETTS

LYMPHOID organs have an important role in the host response to transplanted tissues. Host sensitization and the proliferation of lymphocytes, specifically activated against the graft are thought to occur primarily in the regional lymph node following transplantation of skin allografts, and in the spleen following transplantation of vascularized organ grafts.[24,25] A significant component of these immune reactions is the transport of lymphocytes between the circulating blood and the splenic lymphoid tissues. Recent studies showed a compartmentalization of the lymphocyte population of the spleen: B lymphocytes are primarily found in the marginal zone while T lymphocytes are more centrally located within the periarteriolar sheath.[12,20] Earlier investigations indicated that lymphocyte migration from the blood into the splenic tissues takes place in the periarteriolar sheath; these migrating lymphocytes are mostly T type.[8,9,11,22] While labeled lymphocytes which enter the spleen may leave the splenic tissues via lymphatics, the majority exit through the splenic vein.[7,8]

In order to understand the microcirculatory morphologic basis of immune reactions of the splenic lymphoid tissues, we have investigated the microcirculation of the white pulp of the spleen using microangiography and clearing methods.

MATERIAL AND METHOD

Laparotomy was performed on 25 Sprague-Dawley rats weighing 350 to 450 gm. using intraperitoneal general anesthesia (sodium pentobarbital, 0.1 ml./100 gm.). A PE-90 polyethylene catheter was placed in the abdominal aorta with its tip slightly above the renal arteries. The abdominal viscera were only minimally disturbed and no attempt was made to identify or observe the spleen. The contrast agent was yellow or white silicone rubber containing lead chromate (Microfil) which renders it radiopaque. When catalyzed, the silicone rubber hardens in approximately 30 minutes, providing an excellent cast which can be observed visually or on a roentgenograph. The viscosity of the contrast medium is approximately 25 centipoises. The amount of injection varied from 2 to 20 ml. In 15 animals the splenic or portal vein was transsected prior to the infusion to prevent venous backflow. In this group, 3 animals each received 2, 4, 5, 6, and 10 ml. of contrast agent. In 10 animals the splenic and portal veins were kept intact. The inferior vena cava was cannulated in addition to the aorta, and the venous return was collected. After the injection of more than 2 ml. of Microfil, the animals died. Following hardening of the Microfil, the spleen was removed, weighed, inspected, photographed, and radiographed. After being fixed for 24 hours in 10 per cent buffered formalin, the specimen was dehydrated in increasingly concentrated ethyl alcohol solutions and cleared in methyl salicylate. The cleared specimens were studied under a stereomicroscope and later sectioned both in the transverse and longitudinal direction in thicknesses varying from 300 to 1,500 μ. They were then photographed under a microscope using magnification of 10 to 100×.

The thick sections were placed on a high-resolution Kodak photographic plate and radiographed with a beryllium window

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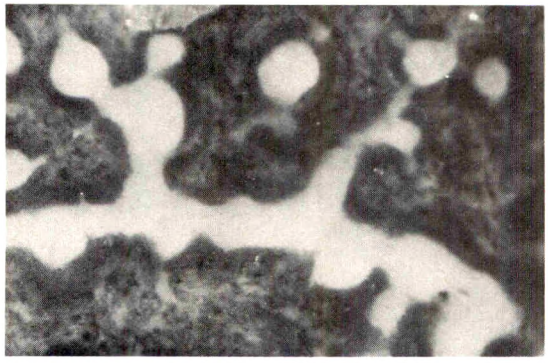

FIG. 1. Longitudinal cut section of the spleen. Note the continuity of the white pulp and its surrounding marginal zone outlined by the india ink (15×).

x-ray tube. The average exposure factors were 20 ma, 15 kv., 40 cm. target-to-tube distance, and an exposure time of approximately 5 minutes. The exposed plates were developed in a D-19 developer and studied under the light microscope.

RESULTS

TERMINOLOGY

In the description of our findings we adopted the following terminology: *white pulp* represents the lymphoid tissues of the spleen including the periarterial sheath and the malpighian corpuscles. The *marginal zone* is the layer of tissue between the white and red pulps. The *central artery* is the arterial structure within the white pulp. The vascular channels present in the marginal zone are called marginal sinus. *Red pulp* is present throughout the spleen outside the marginal zone.

FINDINGS

The white pulp and the surrounding marginal zone formed a continuous tissue mass of fingerlike projections with closely juxtaposed globular structures situated around the central artery (Fig. 1; and 2). The arteries of the white pulp originated from the trabecular artery and became the central artery as they entered the lymphoid tissues of the spleen. The central artery had an average diameter of 40 μ during its course within the white pulp and gave off arterioles measuring approximately 25 μ in diameter and capillaries measuring 8 to 15 μ in diameter. Most of the capillaries of the white pulp terminated in the marginal zone. Occasional capillaries apparently ended blindly within the tissues of the white pulp (Fig. 3).

Within the marginal zone was the marginal sinus, a rich network of short interconnecting irregular channels (Fig. 3; and 4). The thickness of the network varied from 20 to 70 μ (Fig. 5). The marginal sinus was sharply delineated both medially toward the white pulp and laterally toward the red pulp. However, there were occasional connections with red pulp venous sinuses. In most instances, no venous flow from this network could be identified. Veins could not be identified within the white pulp.

When less than 3 ml. of silicone rubber was injected into the aorta, the filling to the vascular structures was limited to the white pulp and the marginal sinus. In addition, the arterial branches left the white pulp and divided into penicilli arteries within the red pulp (Fig. 2). When more than 3 ml. was injected into the aorta, the venous sinusoids of the red pulp and the splenic vein became opacified (Fig. 6).

A detailed evaluation of the microcirculation of the red pulp was not carried out at this time. However, in those experiments where the splenic or portal vein was transsected, both the penicilli arteries and venous sinusoids were well filled, but gen-

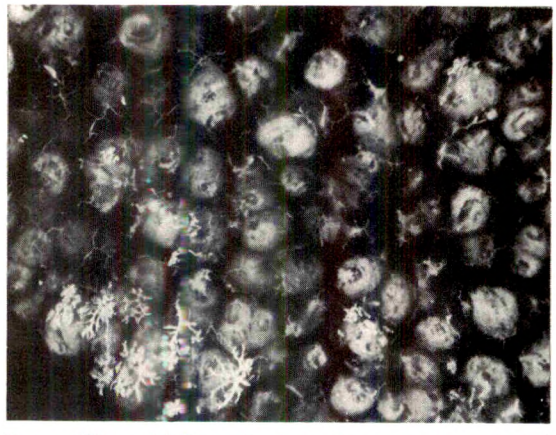

FIG. 2. Cleared injected spleen observed through the cortex. The marginal sinus of malpighian corpuscles is seen as distinct balls.

erally the morphologic continuity of the channels between the arteries and veins could not be established. Often, however, the penicilli arteries formed a capillary network and these capillaries could then be followed to the venous sinusoids. This pattern was commonly seen close to the surface of the spleen (Fig. 7). In those experiments where the venous circulation remained intact, most of the veins filled in a retrograde fashion via the portal vein. After selective retrograde venous injection, we observed opacification of the venous sinusoids without filling of the red pulp capillaries or the marginal zone network (Fig. 8).

Somewhat irregular, large channels were seen within the periarteriolar sheath of the white pulp. Their diameters were approximately 2 to 3 times that of the adjacent central artery (Fig. 3; and 4). The origin of these channels is not clear; however, morphologically they closely resemble the lymphatic vessels observed by Snook.[26] It is very likely that filling originated from small areas of extravasation within the white pulp (Fig. 5).

DISCUSSION

In previous studies of the splenic microcirculation, 3 basic methods were applied. Reconstruction from serial histologic sections was performed by numerous investigators.[5,15,16,28,31–34] A variation of this method includes prior injection of a biologically active substance such as india ink which helps to outline vascular endothelium and other areas which have active phagocytosis (marginal zone).[1,10,19,23,27,29]

A second approach involves *in vivo* transillumination. Meaningful physiologic data can be obtained in addition to morphologic information.[14,17,21] Because only the subcapsular area can be properly illuminated, this method is limited to the study of the red pulp, as the white pulp does not extend peripherally enough for visual observation.

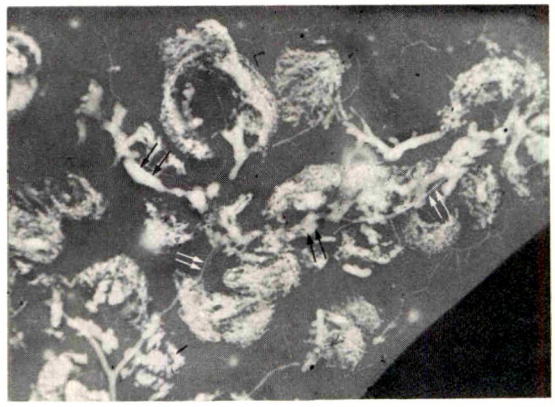

Fig. 4. Microradiograph of a 400 μ cross section (20×). Note the short interconnecting irregular channels forming the marginal sinus. White arrows = central artery; black arrows = lymphatic channels.

Fig. 3. Cross section through the cleared white pulp (30×). The central artery (arrowheads) gives off capillaries which fill the marginal sinus. Partial filling of 2 lymphatic channels (arrows) adjacent to the central artery. No venous connection of the marginal sinus can be identified.

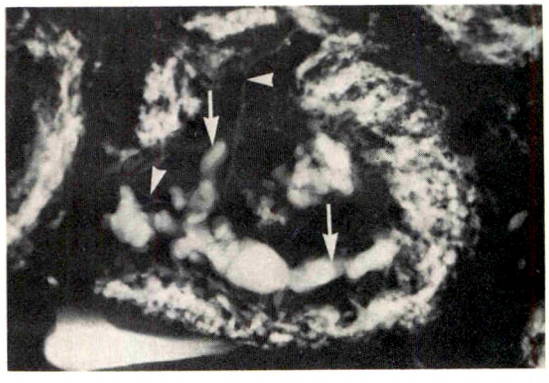

Fig. 5. Microradiograph of a malpighian corpuscle with its surrounding marginal sinus (80×). Central artery (arrowhead); lymphatic channels (arrows).

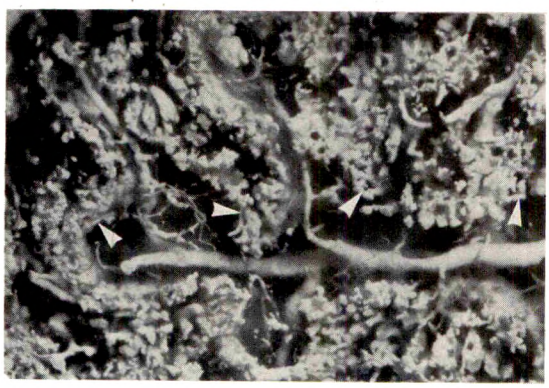

FIG. 6. Longitudinal section of a cleared specimen. Note the central artery, the capillaries of the white pulp, the marginal sinus (arrowheads), and the well-filled red pulp sinusoids (25×).

A third method is dependent on injection of colored or radiopaque substances intravascularly followed by histologic or microradiographic examination.[2–4,7,30]

In this investigation the intravascular injection demonstrates flow within the vessels without specifically showing their wall structures. In this respect, this method is closer to observations made at the time of transillumination than histologic reconstructions. Stereomicroscopic study of injected, cleared specimens provides a 3-dimensional view of the splenic microcirculation in continuity, which is almost impossible to obtain otherwise. Microangiography complements this approach providing sharp images at greater depth than direct vision offers.

Our concept of white pulp circulation is summarized in Figures 9 and 10. The white pulp microvasculature is separated into central and peripheral compartments. The centrally located lymphoid tissues formed a continuous mass surrounding the central arteries and were supplied by loosely arranged capillaries. On the periphery, however, there was a dense and thick vascular network completely surrounding the white pulp. This vascular envelope originates in the white pulp capillaries and has only insignificant venous drainage. The venous flow of the marginal sinus is not clear. Occasional connections between the marginal sinus and the red pulp veins were present but we did not observe connections with the Billroth cords as suggested by others.[6,35]

The microcirculatory morphology of the marginal sinus would indicate slow blood flow which could be advantageous for the transvascular migration of lymphocytes. The re-entry of cells from the white pulp into the blood circulation may occur via connecting bridges through the marginal zone.[18] Another potentially significant route of drainage could be through the large periarteriolar lymphatic channels which were

FIG. 7. In the red pulp, there is a meshwork of tortuous capillaries draining into a venous sinus (25×).

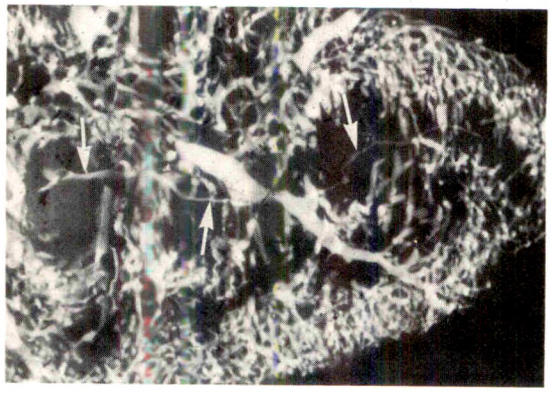

FIG. 8. Micrograph showing retrograde filling of the red pulp veins. Note the lack of filling of the marginal sinus. Small amounts were also injected into the central artery (arrows) (15×).

regularly observed in this study and also described by others.[10,13,26]

CONCLUSION AND SUMMARY

Based on the microangiographic study of injected and cleared rat spleen specimens, we developed a model of the microvasculature of the white pulp (Fig. 10).

The central artery and its arteriolar and capillary branches form a loosely spaced network in the periarteriolar sheath and malpighian corpuscles. From these channels, a rich and thick network of vessels is formed in the marginal zone which completely surrounds the lymphoid tissue mass of the spleen. This marginal sinus network has only poorly developed venous drainage towards the red pulp sinusoids. The microvascular morphology of the marginal sinus implies slow blood flow and this in turn could promote transvascular migration of lymphocytes. Because of the lack of venous flow from the white pulp, the only significant re-entry route to the venous circulation is the rather large periarteriolar lymphatic channels which were observed in this study.

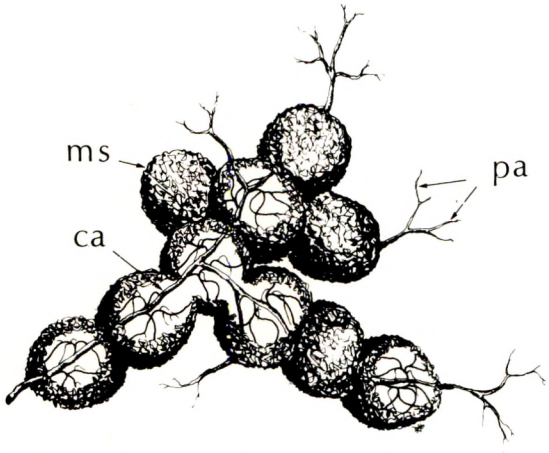

Fig. 9. Semidiagrammatic representation of the white pulp circulation. Note the periarteriolar lymphoid tissues and the malpighian corpuscles which form a continuous structure completely enveloped by the marginal sinus. Note also the marginal sinus completely surrounding the white pulp. ca = central artery; ms = marginal sinus; pa = penicilli arteries.

Fig. 10. Diagrammatic representation of the white pulp microcirculation. ca = central artery; ms = marginal sinus, close anastomosing irregular channels filling from capillaries branching off the central artery; ve = veins of the red pulp: note few direct connections between the marginal sinus and the red pulp veins; LL = lymphatic channels around the central artery; pa = penicilli arteries originating from the central artery.

Our model of the microcirculation of the splenic lymphoid tissues can serve as a morphologic basis of the understanding of the lymphocyte transport in the spleen.

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EDITORIAL

A Resolution

WHEREAS, Dr. Traian Leucutia has chosen to conclude his long service as Editor of the AMERICAN JOURNAL OF ROENTGENOLOGY, RADIUM THERAPY AND NUCLEAR MEDICINE; and

WHEREAS, his service to the Journal spans a period of 50 years beginning in 1924 as an assistant for abstracts, proceeding to Abstract Editor and finally to Editor, a post he has held since1961; and

WHEREAS, his service to the American Roentgen Ray Society has been marked by his election as member in 1930, as President in 1961 and his selection as Caldwell Lecturer in 1960; and

WHEREAS, his contributions elsewhere in radiology have been recognized by his selection as Trustee of the American Board of Radiology and as Gold Medalist of the American College of Radiology; and

WHEREAS, he has faithfully maintained the scientific excellence and pre-eminence of the Journal with his personal characteristics of friend, compassionate physician, constructive yet critical taskmaster and scholar;

THEREFORE, BE IT RESOLVED, that the American Roentgen Ray Society in executive session at its Seventy-Fifth Annual Meeting express its continuing gratitude for his devoted service; and

BE IT FURTHER RESOLVED, that a copy of this resolution be spread upon the minutes and a copy be presented to Dr. Traian Leucutia.

September 24, 1974
San Francisco, California

PAUL A. RIEMENSCHNEIDER, M.D.
Chairman, Publication Committee
American Roentgen Ray Society

NEWS ITEMS

OFFICIAL AMERICAN DELEGATION TO THE XI INTER-AMERICAN CONGRESS OF RADIOLOGY

The following are the names of the elected representatives of the various American societies of radiology who will form an official delegation to the XI Inter-American Congress of Radiology, in Bogotá, Colombia, Feb. 16–21, 1975: Victor P. Bond, M.D., Radiation Research Society; Luther W. Brady, M.D., American Society of Therapeutic Radiologists; Victor A. Marcial, M.D., American Radium Society; Clyde A. Stevenson, M.D., American Roentgen Ray Society; Manuel Viamonte, Jr., M.D., Radiological Society of North America; and Juan A. del Regato, M.D., American College of Radiology, *Chairman*.

NEW OFFICERS OF THE RADIOLOGICAL SOCIETY OF NORTH AMERICA

At the Sixtieth Annual Meeting of the Radiological Society of North America held December 1–6, 1974, at the Palmer House in Chicago, Illinois, the following officers were elected: *President*, John W. Beeler, M.D., Indianapolis, Indiana; *President-Elect*, R. Brian Holmes, M.D., Toronto, Ontario; *First Vice-President*, Howard C. Burkhead, M.D., Evanston, Illinois; *Second Vice-President*, Owings W. Kincaid, M.D., Rochester, Minnesota; *Third Vice-President*, Gwilym S. Lodwick, M.D., Columbia, Missouri; *Secretary*, Theodore A. Tristan, M.D., Harrisburg, Pennsylvania; *Treasurer*, Harold O. Wyckoff, Ph.D., Rockville, Maryland; and *Historian*, William R. Eyler, M.D., Detroit, Michigan.

The Chairman of the Board of Directors is J. W. J. Carpender, M.D., Sayre, Pennsylvania.

The Gold Medal of the Society was awarded to Stanley M. Wyman, M.D., Belmont, Massachusetts; and Richard H. Marshak, M.D., New York, New York.

The Sixty-first Annual Meeting of the Society will be held at the McCormick Place on the Lake, Chicago, Illinois, November 30–December 5, 1975.

AMERICAN SOCIETY OF THERAPEUTIC RADIOLOGISTS (ASTR) OFFICERS FOR 1974–1975

At the 1974 Annual Meeting of the ASTR the following new officers were elected: *President*, Juan A. del Regato, M.D., Tampa, Florida; *President-Elect*, Robert G. Parker, M.D., Seattle, Washington; *Secretary*, Robert W. Edland, M.D., La Crosse, Wisconsin; *Treasurer*, Martin B. Levene, M.D., Boston, Massachusetts; *Members at Large*, John W. Travis, M.D., Topeka, Kansas, and Seymour H. Levitt, M.D., Minneapolis, Minnesota.

The Chairman of the Board of Directors is William T. Moss, M.D., Portland, Oregon.

The 1975 Annual Meeting will be held at the Hyatt Regency Hotel in the Embarcadero Center, San Francisco, California, October 8–12, 1975.

SOCIETY OF GASTRO-INTESTINAL RADIOLOGISTS

At the 1974 Annual Meeting of the Society of Gastro-intestinal Radiologists the following officers were elected: *President*, H. Joachim Burhenne, M.D.; *President-Elect*, Sidney W. Nelson, M.D.; *Past President*, William B. Seaman, M.D.; *Secretary-Treasurer*, John R. Amberg, M.D., University Hospital, 225 W. Dickinson St., San Diego, Calif. 92103; *Directors*, Robert N. Berk, M.D., and Bernard S. Wolf, M.D.

The 1975 Annual Meeting will be held at the Hilton Head Island, 43 miles from Sea Pines Plantation, September 27–29, 1975, preceding the 1975 ARRS meeting at Atlanta. The registration is limited to 175 registrants.

For further information, please write to: H. Joachim Burhenne, M.D., Children's Hospital of San Francisco, P.O. Box 3805, San Francisco, California 94119.

CORRECTION

Inadvertently, the affiliations of Dr. Giovanni Di Chiro were misrepresented in the November, 1974, issue of the JOURNAL. He is Head of the Section on Neuroradiology, National Institutes of Health in Bethesda; Clinical Professor of Radiology at Georgetown University, and Clinical Professor of Neuroradiology at George Washington University, both in Washington, D. C. No slight was intended.

ADVANCED CLINICAL APPLICATIONS OF THE GAMMA SCINTILLATION CAMERA

The Indiana University School of Medicine, Indianapolis, Indiana, announces a 3 day workshop on this topic March 13–15, 1975.

The Course Director is Henry Wellman, M.D., Professor of Radiology and Medicine —Director, Section of Nuclear Medicine.

For further information and applications, please write: Division of Postgraduate Medical Education, Indiana University School of Medicine, 1100 West Michigan Street, Indianapolis, Indiana 46202.

HORMONES AND CANCER

A clinical Cancer Seminar sponsored by the Division of Radiation Therapy, Department of Radiology, and Comprehensive Cancer Center of Greater Miami, will be held at the Americana of Bal Harbour Hotel, Miami Beach, Florida, March 10–14, 1975.

For further information, please write: Komanduri K. N. Charyulu, M.D., Division of Radiation Therapy, University of Miami School of Medicine, P.O. Box 520875 Biscayne Annex, Miami, Florida 33152.

POSTGRADUATE COURSE ON RADIOLOGY OF THE CHEST

The Department of Radiology of New York Medical College will give a Postgraduate Course on Radiology of the Chest at the Plaza Hotel, Fifth Avenue at 59th Street, New York, New York, April 7–9, 1975.

For further information, please contact: Richard M. Friedenberg, M.D., Professor and Chairman, Department of Radiology, New York Medical College, 1249 Fifth Avenue, New ork, New York 10029.

COLUMBIA UNIVERSITY: FOUR DAYS OF NUCLEAR MEDICINE

A Postgraduate Symposium, under the direction of Philip M. Johnson, M.D., Professor of Radiology, Director, Nuclear Medicine, will be held at the Waldorf-Astoria Hotel, New York, New York, April 7–10, 1975.

In addition to the Faculty of the College of Physicians and Surgeons, the Guest Faculty includes: S. James Adelstein, M.D., Ph.D.; Harold L. Atkins, M.D.; David V. Becker, M.D.; Richard S. Benua, M.D.; M. Donald Blaufox, M.D., Ph.D.; Frederick J. Bonte, M.D.; Leonard M. Freeman, M.D.; Stanley J. Goldsmith, M.D.; Alexander Gottschalk, M.D.; David E. Kuhl, M.D.; Lester M. Levy, M.D.; Malcolm D. Powell, M.A.; Leonard Rosenthall, M.D.; Theodore J. Stahl, M.D.; and Gopal Subramanian, Ph.D.

Category I A.M.A. Award: Approved for 26 hours.

For further information, please contact: Philip M. Johnson, M.D., Columbia University, College of Physicians & Surgeons, Box 153, 622 West 168th Street, New York, New York 10032.

POSTGRADUATE COURSE IN PULMONARY RADIOLOGY

This course is presented by the Indiana University School of Medicine, Indianapolis, Indiana, April 23–25, 1975.

All sessions will be held at the Hilton Hotel. A block of rooms has been reserved.

This Continuing Medical Education activity is acceptable for 18 credit hours in Category I for the Physician's Recognition Award of the A.M.A. The program is also

acceptable for 18 hours credit by the American Academy of Family Physicians. The ACGPOMS has approved this course on an hour for hour basis.

In addition to the Local Faculty, the distinguished Guest Faculty includes: Drs. Bookstein, Campbell, Greenberg, Macpherson, Miller, Moser, Rosenow, Stead, Westcott, and Wiot.

For further information, please contact: Indiana University School of Medicine, Division of Postgraduate and Continuing Medical Education, 1100 West Michigan Street, Indianapolis, Indiana 46202.

NEW ORLEANS RADIOLOGY SOCIETY SPRING ROENTGEN CONFERENCE

The New Orleans Radiology Society presents its third Annual Spring Roentgen Conference at Marriott Hotel, New Orleans, Louisiana, May 1–3, 1975.

The Guest Faculty includes: E. Robert Heitzman, M.D., Syracuse, New York, for Chest; Edward B. Singleton, M.D., Houston, Texas, for Pediatrics; Arthur R. Clemett, M.D., New York, New York, for Gastro-Intestinal Tract; George R. Leopold, M.D., San Diego, California, for Ultra Sound; Robert E. Wise, M.D., Boston, Massachusetts, for A.C.R. Activities; and Anthony F. Lalli, M.D., Cleveland, Ohio, for Genito-Urinary Tract; in addition to local participants Roger H. Tutton, M.D., and Lesley M. Warshaw, M.D.

For further information, please write: Abner M. Landry, M.D., New Orleans Radiology Society, P.O. Box 19024, New Orleans, Louisiana 70179.

POSTGRADUATE COURSE IN PEDIATRIC RADIOLOGY

A Postgraduate Course in Pediatric Radiology, sponsored by the Department of Radiology of the Albert Einstein College of Medicine, will be held May 12–16, 1975.

The course has been approved for Category I Credit for the A.M.A. Physician's Recognition Award.

For further information, please contact: Mrs. Claire Delman, Program Administrator, Radiology Postgraduate Course, Albert Einstein College of Medicine, Bronx, New York 10461.

REFRESHER COURSE IN THE PHYSICS AND RADIATION BIOLOGY OF DIAGNOSTIC RADIOLOGY AND NUCLEAR MEDICINE

This course will be offered in Dallas, Texas, May 21–24, 1975.

Co-sponsors are the Radiology Department of Southwestern Medical School and the A. Webb Roberts Center for Continuing Education of the University of Texas Health Science Center at Dallas.

The course is designed for residents preparing for board examinations and for radiologists seeking information on current knowledge and trends in the basic radiologic sciences. The course is acceptable for 24 hours credit under Category I for the A.M.A. Physician's Recognition Award.

The faculty will include, Donald E. Carlson, Ph.D., Edward E. Christensen, M.D., Thomas S. Curry, III, M.D., Glenn V. Dalrymple, M.D., J. Edward Dowdey, Ph.D., Mary Esther Gaulden, Ph.D., William R. Hendee, Ph.D., and Robert W. Parkey, M.D.

The number of enrollees is limited to 60 in the order of enrollment.

For further information, please write: Mary Esther Gaulden, Ph.D., Department of Radiology, Southwestern Medical School, 5323 Harry Hines Boulevard, Dallas, Texas 75235.

ABDOMINAL ULTRASOUND COURSE

The newly emerging subspecialty of abdominal ultrasound will be covered in an intensive 2 day course, presented by the Department of Radiology of Harvard Medical School at the Copley Plaza Hotel in Boston, May 22–23, 1975.

A distinguished international faculty will cover the topic in detail, describing the current state-of-the-art, and the new directions for the future. The format will be 3

half-day sessions of lectures and a half day of informal sessions where course participants may meet with faculty and pursue extended discussions of mutual interest.

An opportunity will be provided during the course to see and use the various scanners available on the commercial market so that questions concerning equipment may be discussed with the faculty on an informal basis.

The faculty includes: Gilbert Baum, M.D.; Ross E. Brown, M.D.; Barry B. Goldberg, M.D.; Hans H. Holm, M.D.; George Kossoff, M.E.; Padmakar P. Lele, M.D.; George R. Leopold, M.D.; Royal J. Bartrum, Jr., M.D.; Carl J. D'Orsi, M.D.; Kenneth Scheer, M.D.; and Edward H. Smith, M.D.

The course is approved for 12½ hours of Category I Credit towards the A.M.A. Physician's Recognition Award.

For further information, please contact: Herbert L. Abrams, M.D., Department of Radiology, Harvard Medical School, 25 Shattuck Street, Boston, Massachusetts 02115.

VOIES BILIAIRES, 75

Under the aegis of the European Association of Radiology and some European Societies for Radiology, Gastro-Enterology, Endoscopy and Nuclear Medicine, a Conference on Biliary Tract, is organized in Bordeaux (University of Bordeaux II), September 4–7, 1975.

The important place which industrial research in these branches occupies prompts an exhibition of new radiologic, endoscopic and nuclear instruments and of pharmacological products, contrast media, hepatic drugs, etc.

The general organization is in charge of WELCOME, a Public Relations Agency which is at disposal for any further information.

For further information please contact: M. de Professeur Delorme, Hopital Sainte-Andre 3, rue Jean-Burguet, 33075 Bordeaux Cedex (France).

It is with deep regret that we announce the death of Ross Golden, M.D., Past President and Life Member of the American Roentgen Ray Society, at Saddleback Hospital in Santa Ana, California, on January 10, 1975.

It is also with deep regret that we announce the death of William David Coolidge, Ph.D., on February 3, 1975. Dr. Coolidge died at his home, 1480 Lenox Road, Schenectady, New York, after a short illness, at 101 years of age. He was the inventor of the Coolidge tube in 1913, a world-famous scientist, and Honorary Member of the American Roentgen Ray Society (1915) and the American Radium Society (1921).

BOOK REVIEWS

Tumors of the Extra-adrenal Paraganglion System (Including Chemoreceptors). Atlas of Tumor Pathology, Second Series, Fascicle 9. By George G. Glenner, M.D., Chief, Section on Molecular Pathology, Laboratory of Experimental Pathology, National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, Bethesda, Md.; and Philip M. Grimley, M.D., Head of Ultrastructural Pathology Section, Laboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, Md. Paper. Pp. 90, with many figures. Price, $4.50. Published by the Armed Forces Institute of Pathology, Washington, D. C., under the auspices of Universities Associated for Research and Education in Pathology, Inc., Bethesda, Md. For sale by the American Registry of Pathology, Armed Forces Institute of Pathology, Washington, D. C. 20306, 1974.

This brief book fulfills the high standards of the second series published as *Atlas of Tumor Pathology* by the Armed Forces Institute of Pathology.

The book describes the gross anatomy and distribution of the extra-adrenal paraganglia and details the finer structure as shown by light microscopy and particularly by electron microscopy.

Tumors of the various organs are described individually after a short discussion of the general appearance and anatomical and clinical behavior of these tumors. Differential diagnosis, arteriographic appearance, and treatment are also briefly considered.

The principal thrust is the microscopic appearance of the lesions, and the photomicrographs are beautiful. Anatomical diagrams and a few reproductions of roentgenograms are included as important additions. The value of this volume to a pathologist is obvious. It will also be useful to the neuroradiologist and visceral arteriographer.

E. Frederick Lang, M.D.

Major Problems in Childhood Cancer. Edited by Carl Pochedly, M.D., Director, Pediatric Hematology, Nassau County Medical Center, East Meadow, Long Island, N. Y.; and Thomas F. Necheles, M.D., Ph.D., Chief, Pediatric Hematology, New England Medical Center Hospitals; Associate Professor of Pediatrics, Tufts University School of Medicine, Boston, Mass. With a foreword by Sydney S. Gellis, M.D. Cloth. Pp. 379, with many illustrations. Price, $14.75. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill. 62617, 1973.

In this book, the authors have attempted to present a comprehensive review of the field of pediatric oncology. Chapters are devoted to all major pediatric disease categories and, in addition, one is devoted to tumor immunology and potentials of immunotherapy.

Notably lacking are chapters reviewing pertinent aspects of cell biology and kinetics, general principles of chemotherapy and a review of modern radiation therapy. Finally, a discussion of the critical area of nursing of often critically ill children undergoing intensive therapy is not included. With the exception of the review chapter on immunotherapy, major deficits are evident throughout this book. A number of factual errors are present such as inclusion of fatigue (p. 68) as a systemic symptom of lymphoma. The histologic discussion of childhood non-Hodgkin's lymphoma is outdated as is the discussion on the role of radiation therapy and chemotherapy for rhabdomyosarcoma. New, promising approaches for the treatment of osteosarcoma are not discussed. Several other areas where major advances have been made are not mentioned or sketchily presented (*i.e.*, non-Hodgkin's lymphoma, Ewing's tumor).

In summary, this book has significant deficits which limit its usefulness for the current management of pediatric neoplasms.

J. Robert Cassady, M.D.

BOOKS RECEIVED

Diagnostic Ultrasound. Edited by Donald L. King, M.D., Associate Professor of Radiology, Columbia University, College of Physicians and Surgeons; Director, Division of Ultrasound, Presbyterian Hospital, Columbia-Presbyterian Medical Center, New York, N. Y. Cloth. Pp. 311, with many illustrations. Price, $42.50. C. V. Mosby

Company, Publishers, 3301 Washington Boulevard, St. Louis, Mo. 63103, 1974.

FUNDAMENTALS OF ORTHOPAEDICS. Second edition. By John J. Gartland, M.D., James Edwards Professor of Orthopaedic Surgery and Chairman of the Department, Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pa. Cloth. Pp. 434, with 193 illustrations. Price, $13.50. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. 19105, 1974.

REVIEW OF ALLIED HEALTH EDUCATION: 1. General Editor, Joseph Hamburg; Associate Editors, Darrel J. Mase and J. Warren Perry. Cloth. Pp. 234. Price, $7.50. The University Press of Kentucky, Lexington, Ky. 40506, 1974.

CURRENT CONCEPTS IN BREAST CANCER AND TUMOR IMMUNOLOGY. Proceedings of the San Francisco Cancer Symposium of 1973. Edited by Joseph R. Castro, M.D., Chief, Department of Radiation Oncology, Claire Zellerbach Saroni Tumor Institute, Mount Zion Hospital and Medical Center; Clinical Professor of Radiology (Radiation Oncology), University of California Medical Center, San Francisco, Calif.; Associate Editors, Thomas S. Meyler, M.D., Associate Chief, Department of Radiation Oncology, Claire Zellerbach Saroni Tumor Institute, Mount Zion Hospital and Medical Center; Assistant Clinical Professor of Radiology (Radiation Oncology), University of California Medical Center, San Francisco, Calif.; and Donald G. Baker, Ph.D., Head, Division of Oncologic and Radiobiologic Research, Claire Zellerbach Saroni Tumor Institute, Mount Zion Hospital and Medical Center. Paper. Pp. 272, with many illustrations. Price, $15.00. Medical Examination Publishing Co., Inc., 65-36 Fresh Meadow Lane, Flushing, N. Y. 11365, 1974.

CARDIAC CATHETERIZATION AND ANGIOGRAPHY. Edited by William Grossman, M.D., Associate Professor of Medicine, University of North Carolina School of Medicine; Director, C. V. Richardson Cardiac Catheterization Laboratory, North Carolina Memorial Hospital, Chapel Hill, N. C. Cloth. Pp. 339, with some illustrations. Price, $24.50. Lea & Febiger, 600 Washington Square, Philadelphia, Pa. 19106, 1974.

NEW TECHNIQUES IN TUMOR LOCALIZATION AND RADIOIMMUNOASSAY. Edited by Millard N. Croll, M.D., Professor of Radiation Therapy and Nuclear Medicine, Hahnemann Medical College, Philadelphia, Pa.; Luther W. Brady, M.D., Professor and Chairman, Department of Radiation Therapy and Nuclear Medicine, Hahnemann Medical College, Philadelphia, Pa.; Takashi Honda, M.D., Associate Professor of Radiation Therapy and Nuclear Medicine, Hahnemann Medical College, Philadelphia, Pa.; and Robert J. Wallner, D.O., Assistant Professor of Radiation Therapy and Nuclear Medicine, Hahnemann Medical College, Philadelphia, Pa. Cloth. Pp. 218, with many illustrations. Price, $19.50. John Wiley & Sons, Inc., Publishers, 605 Third Avenue, New York, N. Y. 10016, 1974.

INTRODUCTION TO RADIOTHERAPY. By Sameer Rafla, M.D., Ph.D., Director of Department of Radiation Therapy, Methodist Hospital, Brooklyn, N. Y.; and Marvin Rotman, M.D., Director of Division of Radiotherapy, Department of Radiology, New York Medical College, New York, N. Y. Cloth. Pp. 177, with 81 illustrations. Price, $11.95. C. V. Mosby Company, Publishers, 3301 Washington Boulevard, St. Louis, Mo. 63103, 1974.

NUCLEAR MEDICINE *In Vitro*. Edited by Benjamin Rothfeld, M.D., Chief, Nuclear Medicine; Associate Chief of Staff for Research and Education; Assistant Chief, Medical Service, Veterans Administration Hospital, Perry Point, Md.; Assistant Professor of Medicine, The Johns Hopkins University School of Medicine, Baltimore, Md. Cloth. Pp. 423, with 137 figures. Price, $29.50. J. B. Lippincott Company, East Washington Square, Philadelphia, Pa. 19105, 1974.

TRAUMA MANAGEMENT. By Edwin F. Cave, Member, Board of Consultation, Massachusetts General Hospital; John F. Burke, Visiting Surgeon, Massachusetts General Hospital; Associate Professor of Surgery, Harvard Medical School; Chief of Staff, Shriners Burns Institute; and Robert J. Boyd, Assistant Orthopedic Surgeon, Massachusetts General Hospital; Clinical Instructor in Orthopedic Surgery, Harvard Medical School. Cloth. Pp. 1,237, with many illustrations. Price, $77.50. Year Book Medical Publishers, Inc., 35 East Wacker Drive, Chicago, Ill. 60601, 1974.

THE RADIOLOGIC CLINICS OF NORTH AMERICA. December, 1974, Volume XII, Number 3. Symposium on Radiology of the Ear. Guest Editor, Guy D. Potter, M.D. Cloth. Pp. 212, with many illustrations. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. 19105, 1974.

SOCIETY PROCEEDINGS

MEETINGS OF RADIOLOGICAL SOCIETIES*

United States of America

American Roentgen Ray Society
Secretary, Dr. James Franklin Martin, 300 S. Hawthorne Rd., Winston-Salem, N. C. 27103. Annual Meeting: Marriott Hotel, Atlanta, Ga., Sept. 30–Oct. 3, 1975.

American Radium Society
Secretary, Richard H. Jesse, Dept. of Surgery, M. D. Anderson Hosp. and Tumor Institute, Houston, Tex. 77025. Annual Meeting: Americana Hotel, San Juan, Puerto Rico, May 4–9, 1975.

Radiological Society of North America
Secretary, Dr. Theodore A. Tristan, Harrisburg, Pennsylvania. Annual Meeting: McCormick Place on the Lake, Chicago, Ill., Nov. 30–Dec. 5, 1975.

American College of Radiology
Executive Director, William C. Stronach, 20 N. Wacker Drive, Chicago, Ill. 60606. Annual meeting: Portland-Hilton Hotel, Portland, Oregon, March 31–April 4, 1975.

Section on Radiology, American Medical Association
Secretary, Dr. Antolin Raventos, Davis, Calif. Annual Meeting: Atlantic City, N. J., June 15–19, 1975.

American Board of Radiology
Secretary, Dr. C. Allen Good. Correspondence should be directed to Kahler East, Rochester, Minn. 55901.

Written Examination will be held in 14 selected sites, June 21, 1975.

Oral examinations will be held: Pittsburgh Hilton, Pittsburgh, Pa., June 2–7, 1975; Statler Hilton, Dallas, Texas, Dec. 8–13, 1975; Marriott Motor Hotel, Chicago, Ill., June 14–19, 1976; Sheraton Biltmore, Atlanta, Ga., Dec. 6–11, 1976.

Applications must be received in the Board Office before Sept. 30 of the year preceding the one in which the candidate wishes to be examined.

Deadline for filing applications for any examination in 1976 is September 30, 1975.

American Board of Nuclear Medicine, Inc. A Conjoint Board of the American Boards of Internal Medicine, Pathology and Radiology and sponsored by the Society of Nuclear Medicine.

Application forms and further information are available from the American Board of Nuclear Medicine, 305 E. 45th St., New York, N. Y. 10017.

American Association of Physicists in Medicine
Secretary, Kenneth D. Williams, M.S., Dept. Radiol., Washington Hospital Center, 110 Irving St., N.W., Washington, D. C. 20010. Annual Meeting.

American Society of Therapeutic Radiologists
Secretary, Dr. Robert W. Edland, 1836 South Ave., La Crosse, Wis., 54601. Annual Meeting: Hyatt Regency Hotel in the Embarcadero Center, San Francisco, Calif., Oct. 8–12, 1975.

American Nuclear Society
Program Chairman, Werner K. Kern, IRD, Space Nuclear Systems, F 309, U. S. Atomic Energy Commission, Washington, D.C. 20545.

American Institute of Ultrasound in Medicine
Secretary, John M. Reid, Ph.D., 556 18th Ave., Seattle, Wash. 98122. Annual Meeting.

American Society of Neuroradiology
Secretary, Dr. David O. Davis, Department of Radiology, 901 Twenty-third St., N.W., Washington, D. C. 20037. Annual Meeting.

Fourteenth International Congress of Radiology
Rio de Janeiro, Brazil, Oct. 23–29, 1977.

International Society of Radiology
Hon. Secretary-Treasurer, Prof. W. A. Fuchs, M.D., Department of Diagnostic Radiology, University Hospital, Inselspital, CH-3010 Bern, Switzerland.

Eleventh Inter-American Congress of Radiology
Counselor for the United States, Dr. Juan A. del Regato, Univ. of South Florida, College of Medicine, Tampa, Fla.
Secretary of Congress, Dr. Alberto Mejia, Apartado Aéreo 53737, Bogotá 2, Colombia. Meeting: Feb. 16–21, 1975.

Inter-American College of Radiology
President, Dr. Miguel Dao y Dao, Apartado Postal 14213, Candelaria, Caracas, Venezuela, S.A.
Secretary of Congress: Dr. Alberto Mejia, Apartado Aéreo 53737, Bogotá 2, Colombia, S.A. Meeting: Bogotá, Colombia, Feb. 16–21, 1975.

Third Congress of the European Association of Radiology
Secretary-General, P.O. Box 14, 79 Lauriston Place, Edinburgh BHI IDB, Scotland, Meeting: June 22–27, 1975.

Second Asian and Oceanian Congress of Radiology
Secretary, Dr. Buenaventura U. V. Angtuaco, Congress Secretariat Headquarters, 2161 Taft Ave., Manila, Philippines. Meeting: Manila, Philippines, Nov. 10–14, 1975.

Alabama Chapter of ACR
Secretary-Treasurer, Dr. Lawrence E. Fetterman, 1720 Springhill Ave., Suite 201, Mobile, Ala. 36604. Meets time and place of Alabama State Medical Association.

Alaska Radiological Society, Chapter ACR
Secretary-Treasurer, Dr. Maurice J. Coyle, 3200 Providence Ave., Anchorage, Alaska 99504.

American Osteopathic College of Radiology
Annual Scientific Meeting: Americana Hotel, Bar Harbor, Fla. Program Administrator: Lawrence J. Jordan, D.O., Suite 21, Ponce American Bldg., 4601 Ponce de Leon Blvd., Coral Gables, Fla. 33146.

American Thermographic Society
Secretary-Treasurer, John Wallace, Ph.D., Dept. Radiol., Thomas Jefferson Univ. Hosp., Philadelphia, Pa. 19107. Annual Meeting.

Arizona Radiological Society, Chapter of ACR
Secretary, Dr. Robert J. Johnson, 1603 N. Tucson Blvd., Tucson 85716. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meeting six months later.

Ark-La-Tex Radiological Society
Secretary, Dr. Erich K. Lang, Confederate Memorial Medical Center, LSU School of Medicine, Shreveport, La. 71101.

Arkansas Chapter of ACR
Secretary-Treasurer, Dr. David H. Newbern, 4301 W. Markham, Little Rock, Ark. 72205. Meets twice annually, the Spring Meeting being in conjunction with and at the place of the State Medical Association.

Association of University Radiologists
Secretary-Treasurer, Dr. Mark M. Mishkin. The Graduate Hosp., Univ. of Pennsylvania, Philadelphia, Pa. 23rd Annual Meeting: San Diego, Calif., May 4–6, 1975.

Atlanta Radiological Society
Secretary-Treasurer, Dr. Marshall J. Cantanzaro, Dept. of Radiol., Northside Hosp., Atlanta, Ga. 30342. Meets on fourth Thursday evenings during the academic year at a

*** Secretaries of societies are requested to send timely information promptly to the Editor.**

time announced in early September of each year, at the Academy of Medicine, Atlanta, Ga., at 8:00 P.M.

BAVARIAN-AMERICAN RADIOLOGIC SOCIETY
Secretary, Maj. Marco J. DiBiase, M.D., Radiology Service, 130th Station Hosp., APO N. Y. 09102.

BLOCKLEY RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Joseph H. Rosen, West Park Hospital, 3905 Ford Rd., Philadelphia, Pa. 19131.

BLUEGRASS RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Eugene Slusher, Lexington Clinic, 1221 S. Broadway, Lexington, Ky. 40504. The Society meets once each month during the school year.

BRONX RADIOLOGICAL SOCIETY, NEW YORK STATE, CHAPTER ACR
Secretary-Treasurer, Dr. Leon J. Corbin, 1369 Rosendale Ave., Bronx, N. Y. 10472. Meets 4 times a year.

BROOKLYN RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Joshua A. Becker, Downstate Medical Clin., 450 Clarkson Ave., Brooklyn, N. Y. 11203. Meets first Thursday of each month, October through June.

BUFFALO RADIOLOGICAL SOCIETY
Secretary, Dr. George J. Alker, Jr., E. J. Meyer Mem. Hosp., Buffalo, N. Y. 14215. Meets second Monday evening each month, October to May inclusive, at University Club.

CALIFORNIA RADIATION THERAPY ASSOCIATION
Secretary-Treasurer, Dr. James R. Eltringham, Stanford Medical Center, Stanford, Calif. 94304. Meets semiannually in San Francisco and Los Angeles.

CALIFORNIA RADIOLOGICAL SOCIETY, CALIFORNIA CHAPTER OF ACR
Secretary-Treasurer, Dr. John L. Gwinn, 4650 Sunset Blvd., Los Angeles, Calif. 90027.

CATAWBA VALLEY RADIOLOGICAL SOCIETY
Secretary, Dr. Walter Joe Jacumin, P.O. Box 265, Rutherford College, N. C. 28671. Meets the last Thursday of every month, Holiday Inn, Morganton, N. C. at 7:30 P.M.

CENTRAL NEW YORK RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Alfred Brettner, Auburn Mem. Hosp., Auburn, N. Y. 13021. Meets first Monday each month October through May.

CENTRAL OHIO RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Daniel E. Lewis, Grant Hosp., Columbus, Ohio 43215. Meets second Thursday in October, November, January, and March 15, and May 19 at Fort Hayes Hotel, Columbus, Ohio.

CENTRAL TEXAS RADIOLOGY SOCIETY
Secretary-Treasurer, Dr. John M. Stoebner, Scott and White Clinic, Temple, Tex. 76501. Meets the fourth Monday of each month at Ponderosa Hotel, Temple, Tex. at 7:00 P.M.

CHICAGO RADIOLOGICAL SOCIETY, DIVISION OF THE ILLINOIS RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary-Treasurer, Dr. Harold J. Lasky, 55 E. Washington St., Suite 1735, Chicago, Ill. 60602. Meets third Thursday of each month, October to April, except December, at the Bismark Hotel, Chicago, Ill.

CLEVELAND RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Charles M. Greenwald, 7007 Powers Blvd., X-Ray Dept., Parma, Ohio 44129. Meetings at 7:00 P.M. on fourth Monday of October, November, January, February, March and fifth Monday of April.

COLORADO RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary, Dr. Jerome D. Sutherland, 3705 E. Colfax Ave., Denver, Colo. 80206. Meets third Friday of each month at Denver Athletic Club from September through May.

CONNECTICUT VALLEY RADIOLOGIC SOCIETY
Secretary, Dr. Gerald N. LaPierre, 759 Chestnut St., Springfield, Mass. 01107. Meets in April and October.

DALLAS-FORT WORTH RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Richard C. Gasser, 1550 W. Rosedale, Rm. 100, Ft. Worth, Tex. 76104. Meets the 3rd Monday of every month at 6:30 P.M., at the Cibola Inn, Arlington, Tex.

DELAWARE CHAPTER OF ACR
Secretary, Dr. Seymour R. Kaplan, Kent Gen. Hosp., Dover, Del. 19901.

EAST BAY RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Robert L. Stein, 43 Dormidera Ave., Piedmont, Calif. 94611. Meets first Thursday each month, Oct. through May, at University Club, Oakland, Calif.

EAST TENNESSEE RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. George H. Wood, 205 Medical Arts Bldg., Knoxville, Tenn. 37902. Meets in January and September.

FLORIDA RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary, Dr. Paul J. Popovich, 1350 S. Hickory St., Melbourne, Fla. 32901. Meets twice annually, in the spring with the Annual State Society Meeting and in the fall.

FLORIDA WEST COAST RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. James P. Ahearn, 501 E. Buffalo Ave., Tampa, Fla. 33603. Meets on 4th Thursday of the months January, March, May, October, and November.

GEORGIA RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary, Dr. E. P. Rasmussen, Piedmont Prof. Bldg., 35 Collier Rd., N.W., Atlanta, Ga. 30309.

GREATER CINCINNATI RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Owen L. Brown, 2421 Auburn Ave., Cincinnati, Ohio 45219.

GREATER KANSAS CITY RADIOLOGICAL SOCIETY
President-Secretary, Dr. Keith W. Gallehugh, Bethany Med. Center, Kansas City, Kans. Meets 5 times a year.

GREATER LOUISVILLE RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. L. D. LeNeave, 315 E. Broadway, Louisville, Ky. 40202. Meets monthly.

GREATER MIAMI RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Robert F. Conti, Holy Cross Hosp., Fort Lauderdale, Fla. 33308. Meets monthly, third Wednesday at 8:00 P.M. at various member hospitals, Miami, Fla.

GREATER ST. LOUIS SOCIETY OF RADIOLOGISTS
Secretary-Treasurer, Dr. Donald Callahan, Northland Med. Bldg., Jennings, Mo. 63136.

HAWAII RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary-Treasurer, Dr. Sidney B. W. Wong, Straub Clinic and Hosp., Honolulu, Hawaii 96813. Meets third Monday of each month at 7:30 P.M.

HEALTH PHYSICS SOCIETY
Secretary, Russell F. Cowing, P.O. Box 156, E. Weymouth, Mass. 02189. Annual Meeting.

HOUSTON RADIOLOGICAL SOCIETY
Secretary, Dr. Neill B. Longley, 6436 Fannin, Suite 601, Houston, Tex. 77025. Meets fourth Monday of each month, except June, July, August and December, at 6:00 P.M., at 103 Jesse H. Jones Library Building, Texas Medical Center, Houston, Tex. 77025.

IDAHO STATE RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary-Treasurer, Dr. John H. Truksa, 1605 Park Ave., Nampa, Id. 83651. Meets in the spring and fall.

ILLINOIS RADIOLOGICAL SOCIETY, INC., CHAPTER OF ACR
Secretary, Dr. Robert D. Dooley, Hinsdale Med. Center, Hinsdale, Ill. 60521. Meets in the spring and fall.

INDIANA ROENTGEN SOCIETY, INC., CHAPTER OF ACR
Secretary, Dr. John A. Knote, 716 Carrolton Blvd., West Lafayette, Ind. 47906.

IOWA RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary-Treasurer, Dr. John Huston, Jr., 1948 First Ave., N.E., Cedar Rapids, Iowa 52402. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific session is held in the autumn.

KANSAS RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary-Treasurer, Dr. Ralph H. Baehr, 310 Medical Arts Bldg., Topeka, Kan. 66604. Meets in spring with State Medical Society and in winter on call.

Kentucky Chapter of ACR
Secretary-Treasurer, Dr. Bernard Sams, St. Joseph Infirmary, 735 Eastern Parkway, Louisvlle, Ky. 40217. Meets in April and September.

Kings County Radiological Society
Secretary, Dr. Sidney Hendler, 1880 Ocean Ave., Brooklyn 30, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

Knoxville Radiological Society
Secretary, Dr. Clifford L. Walton, Blount Professional Bldg., Knoxville 20, Tenn. Meetings are held the third Monday of every other month at the University of Tennessee Memorial Research Center and Hospital.

Long Island Radiological Society
Secretary, Dr. Bruce Saxe, 1200 Stewart Ave., Garden City, N. Y. 11533. Meets monthly.

Los Angeles Radiological Society
Secretary, Dr. Isaac Sanders, 1429 Valley View Rd. 13, Glendale, Calif. 91202. Meets second Wednesday of month in September, November, January, April and June at Los Angeles County Medical Association Building, Los Angeles, Calif. Midwinter Radiological Conference. Century Plaza Hotel, Los Angeles, Calif.

Louisiana Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Roger H. Tutton, 1514 Jefferson Hwy., New Orleans, La. 70121.

Louisiana-Texas Gulf Coast Radiological Society
Secretary-Treasurer, Dr. Arnold G. Manske, P.O. Box 3008, Port Arthur, Tex. 71670.

Maine Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Richard W. Taylor, Radiology Department, St. Mary's General Hospital, Lewiston, Maine 04240. Meets in June, September, December and April.

Maryland Radiological Society, Chapter of ACR
Secretary, Dr. David S. O'Brien, Anne Arundel Hosp., Annapolis, Md. 21401.

Massachusetts Radiological Society, Chapter of ACR
Secretary, Dr. Joseph T. Ferrucci, Jr., Massachusetts Gen. Hosp., Boston, Mass. 02114.

Memphis Roentgen Society
Secretary-Treasurer, Dr. Thomas P. Coburn, The University of Tennessee College of Medicine, Department of Radiology, Walter C. Chandler Bldg., 865 Jefferson Ave., Memphis, Tenn. 38163. Meets first Monday Oct. through May at the University Club.

Miami Valley Radiological Society
Secretary, Dr. Bert Must, I.B.M. Bldg., Dayton, Ohio. Meets third Thursday of fall, winter and spring months at 7:30 P.M. at Miami Valley Hospital, Dayton, Ohio.

Michigan Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Francis P. Shea, Harper Hospital, 3825 Brush St., Detroit, Mich. 48201. Meets monthly, first Thursday, October through May, at David Whitney House, 1010 Antietam, at 6:30 P.M.

Michigan Society of Therapeutic Radiologists
Secretary-Treasurer, Dr. Delmar Mahrt, William Beaumont Hosp., Detroit, Mich. 48072. Meets bi-monthly during the academic year.

Mid-Hudson Radiological Society
Secretary-Treasurer, Dr. William D. Stiehm, 37 Flower Hill Rd., Poughkeepsie, N. Y. 12603. Meets 7:00 P.M., first Wednesday of each month, September to May.

Milwaukee Roentgen Ray Society
Secretary-Treasurer, Dr. Thomas C. Lipscomb, 1004 North Tenth St., Milwaukee, Wis. 53233. Meets monthly on fourth Monday, October through May, at University Club.

Minnesota Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Harlan W. Hawkinson, 6 Buffalo Rd., St. Paul, Minn. 55110. Meets twice annually, fall and winter.

Mississippi State Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Edward L. Gieger, 969 Lakeland Dr., Jackson, Miss. 39216. Meets third Thursday, excluding summer months, at the Primos Northgate Rest., Jackson at 6:30 P.M.

Missouri Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Ronald G. Evens, Mallinckrodt Institute of Radiology, 510 S. Kingshighway, St. Louis, Mo. 63110.

Montana Radiological Society, Chapter of ACR
Secretary, Dr. C. H. Agnew, Room 102, Doctors Bldg., Billings, Mont. 59101.

Nebraska Chapter of ACR
Secretary-Treasurer, Dr. Robert Bodmer, Suite 622 Doctors Bdg., Omaha, Neb. 68131. Meets the third Wednesday of the month, Oct. through March, at the Clarkson Hosp., Omaha, Neb. and the fourth Friday of April at the Lincoln Country Club, Lincoln, Neb.

Nevada Radiological Society, Chapter of ACR
Secretary, Dr. Charles F. Veverka, Carson Tahoe Hosp., Carson City, Nev. 89701.

N.E. Society for Radiation Oncology
Secretary, Dr. C. C. Wang, Mass. Gen. Hosp., Boston, Mass. 02114.

New England Roentgen Ray Society
Secretary, Dr. Melvin E. Clouse, 185 Pilgrim Rd., Boston, Mass. 02115. Meets the third Friday of each month, October through April, excluding December, at The Longwood Towers, 20 Chapel Street, Brookline, Mass. at 3:00 P.M. Annual Meeting: May 16, 1975.

New Hampshire Roentgen Ray Society, Chapter of ACR
Secretary-Treasurer, Dr. Edward P. Kane, Claremont Gen. Hosp., Claremont, N. H. 03743. Meets four to six times yearly.

New Mexico Society of Radiologists, Chapter of ACR
Secretary, Dr. W. M. Jordan, 1100 Central Ave. S.E., Albuquerque, N. M. 87106. Four meetings annually, three held in Albuquerque, N. M., and one held at time and place of New Mexico State Medical Society annual meeting.

New Orleans Radiological Society, Inc.
Secretary-Treasurer, Dr. Jimmy L. Mains, P.O. Box 446, Gretna, La. 70053. Meets bimonthly at local restaurants selected by the President. Spring Conference.

New York Roentgen Society
Secretary-Treasurer, Dr. Thomas C. Beneventano, 110 East 210th St., Bronx, N. Y. 10467. Meets monthly on the 3rd Monday at the New York Academy of Medicine at 4:30 P.M. Annual Spring Conference, Waldorf-Astoria Hotel, New York, N. Y., April 24–26, 1975. A.M.A. Cat. I credit. Further information may be obtained from Dr. Albert A. Dunn, Roosevelt Hosp., New York, N. Y. 10019.

New York State Chapter of ACR
Secretary-Treasurer, Dr. Albert F. Keegan, 6 Secor Dr., Port Wash., N. Y. 11050.

North American Society of Cardiac Radiology
Secretary-Treasurer, Dr. Erik Carlson, Univ. Calif., San Francisco, Calif. 94143.

North Carolina Chapter of ACR
Secretary-Treasurer, Dr. Ernest B. Spangler, Wesley Long Hosp., Greensboro, N. C. 27402. Meets twice a year. The Spring Meeting is held at the time of the meeting of the North Carolina Medical Society. The Fall Meeting is held in November at the Mid Pines Club, Southern Pines, N. C.

North Dakota Radiological Society, Chapter of ACR
Secretary, Dr. Pablo Ramos, Box 1618, Bismarck, N. D. 58501. Meets at time of State Medical Association meeting. Other meetings arranged on call of the President.

North Florida Radiological Society
Secretary, Dr. David F. Bew, University Hospital of

Jacksonville, 655 W. Eighth Street, P.O. Box 2751, Jacksonville, Fla. 32203. Meets quarterly in March, June, September and December.

NORTHEASTERN OKLAHOMA RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Theodore J. Brickner, Jr., 5919 S. Gary Place, Tulsa, Okla. 74110.

NORTHEASTERN NEW YORK RADIOLOGICAL SOCIETY
Secretary, Dr. Donald R. Morton, Dept. of Radiology, St. Clare's Hosp., Schenectady, N. Y. 12304. Meets in Albany area on third Wednesday of October, November, March, April, and May.

NORTHERN CALIFORNIA RADIATION THERAPY ASSOCIATION
Secretary-Treasurer, Dr. James R. Eltringham, Stanford Medical Center, Stanford, Calif. 94304. Meets quarterly.

NORTHERN CALIFORNIA RADIOLOGICAL SOCIETY
Secretary, Dr. Mark D. Reiss, 5301 F Street, Sacramento, Calif. 95819. Meets on the fourth Monday of Sept., Nov., Jan., March and May at the Mansion Inn, Sacramento, Calif.

NORTHWESTERN NEW YORK RADIOLOGICAL SOCIETY
Secretary, Dr. Barbara E. Chick, Glens Falls Hospital, Glens Falls, N. Y. 12801.

NORTHWESTERN OHIO RADIOLOGICAL SOCIETY
Secretary, Dr. Doug Ki Cho, 2730 Navarre Ave., Oregon (Toledo), Ohio 43616. Meets 3rd Wednesday from September to May.

OHIO STATE RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary, Dr. Tearle L. Meyer, 175 S. Merkle Rd., Columbus, Ohio 43215.

OKLAHOMA STATE RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary, Dr. George H. Ladd, 4616 Denison, Muskogee, Okla. 74401. Meets in January, May and October.

ORANGE COUNTY RADIOLOGICAL SOCIETY
Secretary, Dr. Marvin A. Rawitch, 600 E. Washington, Santa Ana, Calif. 92701. Meets on fourth Tuesday of the month, excluding June, July, August, and December, at Orange County Medical Association Bldg., Orange, Calif.

OREGON STATE RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary-Treasurer, Dr. Robert E. Craven, P.O. Box 12542, Portland, Ore. 97212. Meets on second Wednesday of month, October through April, at the University Club, Portland, Ore.

ORLEANS PARISH RADIOLOGICAL SOCIETY
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans, La. 70113. Meets second Tuesday of each month.

PACIFIC NORTHWEST RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Betty J. Wood, Dept. of Radiol., Vancouver General Hosp., Vancouver 9, B. C., Canada. Annual Meeting.

PENNSYLVANIA RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary, Dr. Robert B. Funch, Germantown Hosp., Philadelphia, Pa. 19144.

PHILADELPHIA ROENTGEN RAY SOCIETY
Secretary, Dr. Marvin E. Haskin, 230 N. Broad St., Philadelphia, Pa. 19102. Meets first Thursday of each month at 5 P.M., from October to May in Thompson Hall, College of Physicians.

PITTSBURGH ROENTGEN SOCIETY
Secretary, Dr. Klaus M. Bron, Presbyterian-Univ. Hosp., Pittsburgh 15213. Meets second Wednesday of month, September through May, at the Pittsburgh Athletic Association.

RADIATION RESEARCH SOCIETY
Executive Secretary, Richard J. Burk, Jr., 4211 39th St., N.W., Washington, D. C. 20016. Annual Meeting.

RADIOLOGICAL SOCIETY OF CONNECTICUT, INC., CHAPTER OF ACR
Secretary-Treasurer, Dr. Mehdi S. Eslami, 1389 W. Main St., Waterbury, Conn. 06708.

RADIOLOGICAL SOCIETY OF GREATER CINCINNATI
Secretary-Treasurer, Dr. Alvin Nathan, c/o Academy of Medicine, 320 Broadway, Cincinnati, Ohio 45202. Meets first Monday of each month at Cincinnati Academy of Medicine.

RADIOLOGICAL SOCIETY OF NEW JERSEY, CHAPTER OF ACR
Secretary, Dr. Sidney Ketyer, St. Elizabeth Hosp., 225 Williamson St., Elizabeth, N. J. 07207. Meets in Atlantic City at time of State Medical Society meeting and in October or November in Newark, N. J.

RADIOLOGICAL SOCIETY OF RHODE ISLAND, CHAPTER OF ACR
Secretary-Treasurer, Dr. Daniel J. Alves, Rhode Island Hosp., Providence, R. I. 02902.

RADIOLOGICAL SOCIETY OF SOUTHERN CALIFORNIA
Secretary-Treasurer, Dr. Marshall Rowen, Dept. Radiol., St. Joseph Hosp., 1100 Stewart Dr., Orange, Calif. 92668. Meets three times a year, usually October, February and May.

RADIOLOGICAL SOCIETY OF THE STATE OF NEW YORK
Secretary-Treasurer, Dr. John W. Colgan, 273 Hollywood Ave., Rochester, N. Y. 14618.

REDWOOD EMPIRE RADIOLOGICAL SOCIETY
Secretary, Dr. Charles E. Carter, 121 Sotoyome St., Santa Rosa, Calif. 95405. Meets second Monday every other month.

RICHMOND COUNTY RADIOLOGICAL SOCIETY
Secretary, Dr. Donald P. King, 218 Gun Club Rd., Richmond, Va. 23221. Meets first Thursday of each month at various hospitals.

ROCHESTER ROENTGEN RAY SOCIETY, ROCHESTER, N. Y.
Secretary-Treasurer, Dr. Robert J. Bruneau, 1441 East Ave., Rochester, N. Y. 14610. Quarterly meetings on the call of the President, at the Rochester Academy of Medicine.

ROCKY MOUNTAIN RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Lorenz R. Wurtzebach, 4200 E. Ninth Ave., Denver, Colo. 80220. Annual meeting: Brown Palace Hotel, Denver, Colo., Aug. 1975.

SAN ANTONIO-CIVILIAN MILITARY RADIOLOGICAL SOCIETY
Secretary, Dr. James R. Stewart, Oak Hills Medical Ctr., San Antonio, Tex. 78209. Meets third Wednesday of each month at Fort Sam Houston Officers Club at 6:30 P.M.

SAN DIEGO RADIOLOGICAL SOCIETY
President, Dr. Stanley G. Seat, 476 Prospect St., La Jolla, Calif. 92037. Meets the first Wednesday of each month at the University Club.

SAN FRANCISCO RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Charles A. Gooding, Univ. of Calif. Med. Ctr., San Francisco, Calif. 94122.

SECTION ON RADIOLOGY, CALIFORNIA MEDICAL ASSOCIATION
Secretary, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

SECTION ON RADIOLOGY, MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA
Secretary-Treasurer, Dr. Albert M. Zelna, 21 Masters St., Potomac, Md. 20854. Meets at Medical Society Library, third Wednesday of January, March, May and October at 8:00 P.M.

SECTION OF RADIOLOGY, NATIONAL MEDICAL ASSOCIATION
Secretary, Dr. Ruby Brooks, Dept. Radiol., Veterans Adm. Hosp., P.O. Box 511, Tuskogee, Ala. 36083. Annual Meeting.

SECTION ON RADIOLOGY, SOUTHERN MEDICAL ASSOCIATION
Secretary, Dr. Mario A. Calonje, 1514 Jefferson Highway, New Orleans, La. 70121. Annual Meeting.

SECTION ON RADIOLOGY, TEXAS MEDICAL ASSOCIATION
Secretary, Dr. George F. Crawford, St. Elizabeth Hospital, Beaumont, Tex. Meets annually with the Texas Medical Association.

SHREVEPORT RADIOLOGICAL CLUB
Secretary, Dr. W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday at 7:30 P.M., September to May inclusive.

SOCIETY FOR PEDIATRIC RADIOLOGY
Secretary-Treasurer, Dr. John P. Dorst, 601 N. Broadway, Baltimore, Md. 21205. Annual meeting: Marriott Hotel, Atlanta, Ga., Sept. 28–29, 1975.

Society of Gastro-intestinal Radiologists
Secretary-Treasurer, Dr. John R. Amberg, University Hospital, 225 W. Dickinson St., San Diego, Calif. 92103.

Society of Nuclear Medicine
Secretary, Dr. E. James Potchen, Edward Mallinckrodt Institute of Radiology, 660 S. Euclid Ave., St. Louis, Mo. 63110. *Administrative Officer*, Mrs. Margaret Glos, 211 E. 43rd St., New York, N.Y. 10017. Annual Meeting.

South Bay Radiological Society
Secretary, Dr. John H. Callaghan, Redwood Med. Clinic, 2900 Whipple Ave., Redwood City, Calif. 94062. Meets the 2nd Monday of each month at the Santa Clara County Medical Association Bldg., 700 Empey Way, San Jose, Calif.

South Carolina Radiological Society, Chapter of ACR
Secretary, Dr. George W. Brunson, 1406 Gregg St., Columbia, S. C. Annual meeting (primarily business) in conjunction with the South Carolina Medical Association meeting in May. Annual fall scientific meeting at time and place designated by the president.

South Coast Radiological Society Chapter of ACR
Secretary-Treasurer, Dr. Richard T. Love, Santa Barbara Med. Clin., 215 Pesetas Lane, Santa Barbara, Calif. 93110. Meets fourth Tuesday of alternate months, Sept., Nov., Jan., March and May.

South Dakota Radiological Society, Chapter of ACR
Secretary, Dr. M. F. Petereit, 2416 S. Phillips, Sioux Falls, S. D. 57105. Meets in spring with State Medical Society and in fall.

Southern California Radiation Therapy Society
Secretary-Treasurer, Dr. Duane J. Gillum, 250 W. Pueblo St., Santa Barbara, Calif. 93105. Meets quarterly.

Southern Radiological Conference
Secretary-Treasurer, Dr. Marshall Eskridge, Mobile Infirmary, P.O. Box 7544, Mobile, Ala. 36607. Annual Meeting: Grand Hotel, Point Clear, Ala.

Tennessee Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Charles W. Kimsey, 111 Whitehall Bldg., 960 E. Third St., Chattanooga, Tenn. 37403. Meets annually at the time and place of the Tennessee State Medical Association meeting.

Texas State Radiological Society, Chapter of ACR
Secretary, Dr. Francis E. O'Neill, 1128 Nix Prof. Bdg., San Antonio, Tex. 78205.

The Fleischner Society
Secretary, Dr. E. Robert Heitzman, State University of New York Upstate Medical Center, Syracuse, N. Y. 13210. Annual Meeting: St. Francis Hotel, San Francisco, Calif., May 28–31, 1975.

Tri-State Radiological Society
Secretary, Dr. John H. Marchand, Jr., Methodist Hospital, Henderson, Ky. Meets third Wednesday of Oct., Jan., March and May, 8:00 p.m., Elks Club in Evansville, Ind.

Upper Peninsula Radiological Society
Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

Utah State Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Patrick Lester, Dept. Radiol., University of Utah Medical Center, Salt Lake City, Utah 84112. Meets quarterly at Holy Cross Hospital.

Vermont Radiological Society, Chapter of ACR
Secretary, Dr. J. Lorimer Holm, R.R. #3, Barre, Vt. 05641.

Virginia Chapter of ACR
Secretary-Treasurer, Dr. Charles P. Winkler, 3500 Kensington Ave., Suite 2-A, Richmond, Va. 23221.

Washington, D. C., Chapter of ACR
Secretary-Treasurer, Dr. Robert M. Allen, 9312 Convento Terr., Fairfax, Va. 22030.

Washington State Radiological Society, Chapter fo ACR
Secretary-Treasurer, Dr. Donald J. Hesch, 3216 N.E. 45th Place, Seattle, Wash. 98105.

West Virginia Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Andrew W. Goodwin, II, 200 Med. Arts Bldg., Charleston, W. Va. 25301. Meets concurrently with annual meeting of West Virginia State Medical Society, other meetings arranged by program committee.

Westchester County Radiological Society
Secretary, Dr. James O. Richardson, Jr., 280 Mamaronek Ave., White Plains, N. Y. 10605. Meets on second Tuesday of October, December, February and May.

Wisconsin Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. June Unger, Wood VA Hosp., Wood, Wis. 53193. Meets twice a year, May and September.

Wisconsin Society of Therapeutic Radiologists
Secretary, Dr. Alvin Greenberg, Radiother. Ctr., Univ. Hospitals, Madison, Wis. 53706. Meets quarterly.

Wyoming Radiological Society, Chapter of ACR
Secretary, Dr. Ross J. Collie, Box 96, Lander, Wyo. 82520. Meets in fall with State Medical Society and in spring on call of President.

Mexico, Puerto Rico and Central America

Asociación Costarricense de Radiología
Secretary, Dr. Rafael Umaña-Umaña, Apartado 8-5340, San José, Costa Rica.

Asociacón de Radiólogos de Centro America y Panamá. Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá
Secretary-General, Dr. Francisco Miranbell Solis, Apartado 3352, San José, Costa Rica, Central America. Meets annually in a rotating manner in the six countries.

Asociación Puertorriqueña de Radiología
Secretary, Dr. R. B. Díaz Bonnet, Suite 504, Professional Bldg., Santurce, Puerto Rico.

Sociedad de Radiología de Salvador
Secretary, Dr. Carlos Meijia, 5a Av. Nte. No. 434, San Salvador, Rep. El Salvador.

Sociedad de Radiología de Guatemala
Secretary, Dr. Carlos E. Escobar, 9², Calle A 0–05, Zona 1, Guatemala

Sociedad Mexicana de Radiología, A.C.
Coahuila No. 35, México 7, D.F., México.
Secretary-General, Dr. Jorge Cano Coquí. Meets first Monday of each month.

Sociedad Radiológica Panameña
Secretary, Dr. L. Arrieta Sánchez, Apartado No. 6323, Panamá, R. de P. Meets monthly in a department of radiology of a local hospital chosen at preceding meeting.

Sociedad Radiológica de Puerto Rico
Secretary, Dr. Heriberto Pagán Sáez, Box 9387, Santurce, Puerto Rico. Meets second Thursday of each month at 8:00 p.m. at the Puerto Rico Medical Association Bldg. in San Juan.

British Commonwealth of Nations

Association of Radiologists of the Province of Quebec
121 Boul. Taschereau, Greenfield Park, P. Q., Canada. Meets four times a year.

British Institute of Radiology
Honorary Secretaries, D. H. Traspnell, M. Cohen, 32 Welbeck St., London, W1M/7PG, England.

Canadian Association of Physicists, Division of Medical and Biological Physics
Honorary Secretary-Treasurer, Dr. R. G. Baker, Ontario Cancer Foundation, Ottawa Civic Clinic, 1053 Carling Ave., Ottawa 3, Ont., Canada.

Canadian Association of Radiologists
Honorary Secretary, Dr. Ross O. Hill, Suite 806, 1440 St. Catherine St. West, Montreal 107, Que., Canada. Annual Meeting: Toronto, Ont., May 11–16, 1975.

Edmonton and District Radiological Society
Secretary, Dr. L. A. Koller, Suite 360, Professional Bldg., 10830 Jasper Ave., Edmonton 15, Alberta, Canada.

Meets third Thursday of each month October to May, except December, at various Edmonton Hospitals.

FACULTY OF RADIOLOGISTS
Honorary Secretary, J. W. Laws, Lincoln's Inn Fields, London WC2A 3PN, England.

MONTREAL RADIOLOGICAL STUDY CLUB
Secretary, Dr. W. Paul Butt, Montreal General Hospital, Montreal, Que., Canada. Meets first Tuesday evening, October to April.

SECTION OF RADIOLOGY OF THE ROYAL SOCIETY OF MEDICINE (CONFINED TO MEDICAL MEMBERS)
Meets third Friday each month at 8:15 P.M. at the Royal Society of Medicine, 1 Wimpole St., London, W. 1 M8AE, 1 England.

SOCIÉTÉ CANADIENNE-FRANÇAISE DE RADIOLOGIE
Secretary-General, Dr. Hubert Sasseville, Verdun Hospital, Montréal, P. Q., Canada. Meets every third Tuesday from October to April.

THE HOSPITAL PHYSICISTS' ASSOCIATION
Honorary Secretary, J. B. Massey, B.Sc., Christie Hosp. and Holt Radium Institute, Physics Department, Withington, Manchester M20 9BX, England.

TORONTO RADIOLOGICAL SOCIETY
Secretary, Dr. George Wortzman, Toronto General Hosp., Toronto 12, Ont., Canada. Meets second Monday of each month, September through May.

THE ROYAL AUSTRALASIAN COLLEGE OF RADIOLOGISTS
Honorary Secretary, Dr. T. P. Loneragan, 45 Macquarie St., Sydney, N.S.W. 2000, Australia.

SOUTH AMERICA

COLÉGIO BRASILEIRO DE RADIOLOGIA
Secretary-General, Dr. Lauro de Abreu Coutinho, Caixa Postal 5984, São Paulo, Brazil.

FEDERACIÓN ARGENTINA DE SOCIEDADES DE RADIOLOGÍA
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ABSTRACTS OF RADIOLOGIC LITERATURE

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ROENTGEN DIAGNOSIS

Head

Danziger, J., Allen, K. Lewer, and Bloch, S. Intracranial chordomas. *Clin. Radiol.*, July, 1974, *25*, 309–316. (From: The Departments of Radiology and Neurosurgery, Princess Nursing Home, Hillbrow, Johannesburg, Republic of South Africa.)

The authors present a retrospective study of 9 cases of intracranial chordomas and suggest that the growth pattern of this tumor and subsequent symptomatology are dependent upon the site of origin of the tumor on the clivus and, therefore, whether the tumor growth is in a forward or backward and downward direction on the clivus. From this information the radiologist and clinician should be able to predict the consequent clinical and radiographic evolution of the tumor in a patient presenting with early chordoma.

Intracranial chordomas can arbitrarily be divided by behavior into 4 stages: an initial silent or asymptomatic growth phase within the clivus; an active phase when the patient presents with clinical signs and symptoms indicating encroachment upon vital structures; the second latent, but active phase following surgery; and a fourth stage of recurrence with clinical deterioration. Either type of tumor extension is commonly associated with a soft tissue nasopharyngeal mass.

The forward extending group of tumors arises from notochordal remnants in the basiocciput to involve the sphenoid, pituitary fossa, subsequently the optic foramina, superior orbital fissures and orbits and by extradural spread, laterally, into the middle cranial fossa. Initial symptom of a headache due to expansion of tumor within the clivus progresses with sphenoid sinus opacification, complaints referable to the eyes and anosmia due to extension tumor mass into the anterior cranial fossa.

Backward and downward extension of a chordoma from the basiocciput produces destruction of the basiocciput with involvement of the apical ligament and adjacent cervical vertebrae. Earliest extension into the cervical spine is noted on the upper margin of the dens and, with further tumor growth, scalloping occurs along the anterior margins of the upper several cervical vertebrae as the tumor grows along or under the anterior longitudinal ligament. There may be concurrent extension into the prepontine cisterns, with displacement of the brain stem posteriorly. Clinical complaints are referable to compression of the posterior fossa contents, initially due to involvement of the lower cranial nerves, particularly the 12th nerve with dysphasia and dysarthria. Here, destruction of the lower part of the clivus is always evident and commonly associated with calcifications. Further cerebellar signs may then develop.

A single patient presented with conductive deafness due to obstruction of the eustachian tubes by a nasopharyngeal mass and 2 patients complained of pain in the neck subsequent to erosive scalloping in the anterior margin and later destruction of the bodies of the upper cervical vertebrae.—*John T. Underberg, M.D.*

Arzoumanian, Artin, and Rosenthall, Leonard. The combined use of radiopertechnetate and ^{99m}Tc-polyphosphate in distinguishing cerebral and calvarial lesions. *J. Canad. A. Radiologists*, Sept., 1974, *25*, 178–183. (Address: Leonard Rosenthall, M.D., Division of Nuclear Medicine, The Montreal General Hospital, Montreal, Quebec, H3G 1A4, Canada.)

The authors performed head scannings on 30 patients using Tc^{99m} pertechnetate ($Tc^{99m}O_4$) and Tc^{99m} polyphosphate ($Tc^{99m}PP$). The time interval between the 2 studies in each patient was more than 24 hours but less than 1 month.

The lesions included cerebrovascular accidents, intracerebral neoplasms, metastatic disease to bone, and postcraniotomy bone flaps. The aim of their study was to determine if $Tc^{99m}O_4$ had a greater affinity for intracerebral disease than did $Tc^{99m}PP$, and if $Tc^{99m}PP$ had a greater affinity for bone lesions than for intracranial abnormalities.

Of the 30 patients reviewed there were 5 cases in which the combined static $Tc^{99m}O_4$ and $Tc^{99m}PP$ failed to localize the involvement in either the brain or skull according to the anticipated differential concentrations. These cases included 3 with cerebrovascular accidents, and 1 each with multiple myeloma and bronchogenic carcinoma. The remaining 25 patients showed higher uptake of $Tc^{99m}O_4$ than $Tc^{99m}PP$ in cerebral lesions and the reverse in skull lesions and craniotomy flaps.

The authors indicate that, although the series is small, there is good evidence of equal or greater uptake of $Tc^{99m}PP$ than $Tc^{99m}O_4$ in some cases of neoplasia and cerebrovascular accidents. Thus it is concluded that no absolute criteria can be established for the use of these scanning agents in the detection of calvarial and/or intracranial pathology. —*Merle K. Loken, M.D., Ph.D.*

Preimesberger, Kenneth F., Loken, Merle K., and Shafer, Rex B. Abnormal brain scan in Paget's disease of bone—confusion with subdural hematoma. *J. Nuclear Med.*, Oct., 1974, *15*, 880–883. (Address: Rex B. Shafer, M.D., Nuclear Medicine Service, Veterans Administration Hospital, 54th Street and 48th Avenue, S., Minneapolis, Minn. 55417.)

The difficulty in diagnosing subdural hematomas

with the brain scan may manifest as a false-negative diagnosis, which may occur as frequently as 20 per cent of the time, or as a false-positive diagnosis, if the patient has a scalp hematoma, skull fracture, or contusion without subdural collection. In general, when the skull roentgenograms are normal, most of these causes of false-positive diagnosis can be excluded. In particular, Paget's disease is usually not considered as a diagnostic possibility when the roentgenograms are normal.

Two patients with a history of head trauma were evaluated for possible subdural hematoma with brain scan and skull roentgenograms. The scans in both patients revealed increased peripheral activity, with normal skull roentgenograms. One patient had several arteriograms in an effort to find the subdural hematoma. None was found. A bone scan revealed increased tracer concentration in the region of the lesions seen on the pertechnetate examination. Roentgenograms of the lumbar spine in both patients revealed evidence for early Paget's disease.

These studies suggest that Paget's disease must be considered in the differential diagnosis of peripheral lesions of the head, even in the presence of normal skull roentgenograms.—*Wm. H. Strauss, M.D.*

Neck and Chest

Sachdeva, H. S., Chowdhary, G. C., Bose, S. M., Gupta, Brij B., and Wig, J. D. Thyroid lymphography. *A.M.A. Arch. Surg.*, Sept., 1974, *109*, 385–387. (Address: Dr. H. S. Sachdeva, Department of Surgery, Division of General Surgery Unit II, Postgraduate Institute of Medical Education and Research, Chandigarh, India.)

The authors studied the internal architecture of the thyroid glands of 40 patients by means of percutaneous injection of iodized oil. With the neck extended a needle was introduced obliquely into one lobe of the gland and 2 cc. of oil was injected over a period of 3 minutes. The procedure was repeated contralaterally. After removal of the needle local pressure was applied for a few minutes following which anteroposterior and lateral roentgenograms of the neck were taken at 15 minutes, 24 hours and 48 hours after the dye injection. All of the patients had surgery and histologic examination.

A variety of diagnostic situations were encountered including solitary thyroid nodule, multinodular goiter, hyperthyroidism, carcinoma, and hypothyroidism. Over-all accuracy rate was 90 per cent except in solitary nodule, where it was 77 per cent. Cervical lymph nodes were visualized in 70 per cent of instances; however, metastases were not visualized even in instances where the nodes were clinically hard and histologic examination revealed metastatic deposits.

Abstractor's Note.

The authors state that no complications were encountered. The article does not suggest that longterm follow-up or delayed histologic sampling was done in these patients. The possibility of delayed lipogranulomatous reaction with fibrosis and compromise of functioning thyroid parenchyma should be investigated before this procedure is presented as a safe diagnostic technique. In addition one notes no mention of isotopic thyroid scanning to suggest that its accuracy in those cases has been compared to the thyroid lymphography. If safety and greater accuracy are established, this technically simple procedure would be an extremely useful adjunct in management of thyroid disease.—*Rosalind H. Troupin, M.D.*

Bomsel, F., Amiel, C., and Firtion, G. Wilson and Mikity syndrome: (eight cases). *Ann. de radiol.*, May–June, 1974, *17*, 305–315. (Address: Dr. G. Firtion, Centre de Recherches biologiques et néonatales—Hôpital de Port-Royal, 123 bd. de Port-Royal, F 75674 Paris Cedex 14, France.)

The Wilson-Mikity syndrome is a rare chronic respiratory disease affecting premature low birth weight infants. Eight cases were diagnosed between 1967 and 1972 among approximately 3,000 deliveries.

Initial symptoms occurred from 2 days to 2 months of age and included transient respiratory distress, low APGAR scores, repeated apneas and feeding aspiration. One infant had a low pO_2 and cyanosis without respiratory distress or congenital heart disease.

In 6 of 8 cases, suctioning was productive and secondary pulmonary infections occurred within the first month of disease. Initial chest roentgenograms included 3 normals, 1 small right pneumothorax, and 3 diffuse "blurred" opacities with atelectatic areas. The typical roentgenologic findings usually occurred during the first month of life.

The first stage consisted of coarse opacities without apical or basilar sparing with associated cystic areas. The appearance lasted 2–4 weeks, corresponding to the period of productive secretions. The second stage consisted of enlargement and coalescence of cysts with basilar hyperlucency. The densities appeared streaky and radiated from the hila to the upper lobes. An additional radiographic finding was poor mineralization of the ribs with 2 of the 8 cases having fractures. The infants all recovered, with the chest roentgenograms returning to normal between 5 and 18 months after numerous clinical episodes of bronchitis.

The relationship between Wilson-Mikity syndrome and broncho-pulmonary dysplasia was presented. The latter occurs after hyaline membrane disease

and artificial ventilation. The repeated secondary infections may be responsible for the occasionally similar pathologic changes.

Oxygen therapy was utilized in both disease entities. In bronchopulmonary dysplasia, oxygen was administered in high concentration, prolonged low concentration, or combinations. In almost all cases of Wilson-Mikity syndrome, prolonged low concentrations of oxygen were given prior to clinical onset of disease. The authors postulate that the bronchioles react to the increased oxygen concentration by hypersecreting. This, in turn, gives rise to the early clinical and radiologic signs. Treatment should rapidly follow any positive bacterial culture. Postural drainage should be used. Oxygen therapy should be discontinued as soon as possible. The less oxygen used during the first stage of disease, the less severe is the emphysema in the second stage. Early treatment and the judicious use of oxygen contributed to the favorable results in all 8 cases.—*Ronald J. Ross, M.D.*

Steckel, Richard J. The radiolucent kinetic border line in acute pulmonary oedema and pneumonia. *Clin. Radiol.*, July, 1974, *25*, 391–395. (Address: Leo G. Rigler Center for Radiological Sciences, University of California Department of Radiological Sciences, The Center for the Health Sciences, Los Angeles, Calif. 90024.)

The author utilizes 4 case reports to emphasize a consistent radiographic finding noted in patients with pulmonary edema and actively pulsating heart and aortic arch. The finding consists of a uniform 2–3 mm. radiolucent "black line" in edematous lungs immediately adjacent to pulsating mediastinal borders such as the heart or aortic arch. It is emphasized that this thin radiolucent line is not a "silhouette sign" resulting from dependent or dorsal redistribution of the edema fluid in the supine patient, but an actual lucent separation between the mediastinal border and the adjacent edematous lung resulting from the pulsatile activity of the mediastinal vasculature. In certain "hyperkinetic" conditions accompanied by lung edema, such as thyrotoxic heart disease, free aortic insufficiency or high output cardiac failure accompanying severe anemic states, a radiolucent band will be unusually wide or prominent.

The finding can be obscured in unusually severe edema or consolidation of the lung bases, resulting in an essentially airless or drowned lung or in moderately large basal pleural effusions which partially deface the heart borders.

The author concludes that the radiolucent kinetic border line when present adjacent to the heart aorta effectively rules out a "silent" heart border such as seen with a large pericardial effusion.

Case reports of acute pulmonary edema, large alveolar infiltrates in the presence of extensive hypersensitivity pneumonitis and pulmonary edema secondary to homozygous sickle cell anemia, positively demonstrated the kinetic border line, whereas a patient with enlarged cardiac silhouette in association with bilateral pleural effusions and pulmonary edema with pericardial effusion had no kinetic border line.

The author disputes the so-called Mach effect or phenomenon as an untenable explanation for the radiographic findings and believes that an actively pulsating cardiac vascular border may act as a "peristaltic pump" and in effect may milk edematous fluid from the adjacent lung and speed lymphatic return with re-aeration of the neighboring lung. The result is the thin radiolucent black line or halo. A similar mechanism is thought to contribute to the absence of pulmonary edema from the lung periphery and diaphragmatic surfaces of the lungs due to the ventilatory movements of the diaphragm and ribs.—*John T. Underberg, M.D.*

Abdomen

Sugarbaker, Paul H., Vineyard, Gordon C., Lewicki, Ann M., Pinkus, Geraldine S., Warhol, Michael J., and Moore, Francis D. Colonoscopy in the management of diseases of the colon and rectum. *Surg., Gynec. & Obst.*, Sept., 1974, *139*, 341–349. (From: The Departments of Surgery, Radiology, and Pathology, Harvard Medical School at the Peter Bent Brigham Hospital, Boston, Mass.)

This article is of limited interest to radiologists. It is a good preliminary study of the clinical (surgical) management of a variety of colon lesions utilizing the fiberoptic colonoscope.

In comparing the value of barium enema examination to colonoscopy, the article is weak, primarily because the number of cases in each disease category is too small for meaningful analysis.

The authors state "with rare exception, barium enema should always precede colonoscopy," and "We consider barium enema and colonoscopy to be complimentary examinations, each with specific indications."

I fail to understand the specificity of barium enema studies, and I was well aware of our margin of error before reading the article (*i.e.*, of 21 polyps missed by barium enema, 17 were less than 0.5 cm., and 8 were less than 1 cm.).—*Adele R. Altman, M.D.*

Smulewicz, Jan J., and Govoni, Antonio F. Giant air cysts of the colon. *J. Canad A. Radiologists*, Sept., 1974, *25*, 245–250. (Address: Jan J. Smulewicz, M.D., Department of Radiology, Queens Hospital Center, Affiliation of the Long Island Jewish-Hillside

Medical Center, 82-68 164th Street, Jamaica, N.Y. 11432.)

Two additional cases of giant diverticula of the colon are added to the literature, which previously contained only 35 cases. These giant cysts most commonly present in the seventh decade. In the first case it was an incidental finding in the sigmoid region and surgery was refused. The second case came to surgery and the diagnosis was confirmed, having presented with abdominal distention.

A review of the cases reveals that this entity can at times present as a palpable painful abdominal mass with fever and abdominal distention. Occasionally, an acute abdomen can result secondary to abscess formation, perforation, or to volvulus. In a majority of the cases the diverticulum was solitary and in almost all cases the cyst arose from the antimesenteric aspect of the bowel wall and is considered, therefore, to be a false diverticulum.

A discussion of the origin of diverticula followed, with perhaps the most perceptive being that of Fleischner, who concluded that the diverticula arise secondary to intraluminal pressure at the weak spot in the circular muscle where the vasa recta penetrate. Increased pressure may well be present in the sigmoid portion of the colon, where most diverticula originate. The growth of a diverticulum into a giant cyst, such as described in the 2 cases in this paper, may most likely be accompanied by an inflammatory process which accompanies the diverticulum formation when communication with the bowel does not persist.

The differential diagnosis should include duplication of the colon, since these can be found intimately attached at any level of the alimentary canal from tongue to anus. Volvulus can be excluded by barium study and abscess can be defined on a clinical basis. No muscular fibers can be demonstrated in the wall of the giant cyst.—*Robert P. Andrews, M.D.*

MASTERS, STUART J., and RICE, REED P. The homogeneous density of gas in the diagnosis of intra-abdominal abscess. *Surg., Gynec. & Obst.*, Sept., 1974, *139*, 370–374. (From: The Department of Radiology, Duke University Medical Center, Durham, N. C.)

Intra-abdominal abscesses occur most commonly after perforations of a viscus or postoperatively. Clinical recognition may be difficult. Radiographic evaluation is frequently limited to a supine roentgenogram of the abdomen, because of the patient's precarious condition.

A mottled air collection, resembling fecal contents in the colon, is a well-documented appearance of an intra-abdominal abscess. Equal emphasis has been accorded the ill-defined soft tissue mass which may or may not displace adjacent viscera.

The authors describe intra-abdominal abscesses presenting radiographically as homogeneous gas lucencies, which do not change shape with alterations of patient position. The lucencies tend to be round or oval, and have sharply demarcated borders. Their inner margins are devoid of textured, intestinal mucosal patterns. Dilated, atonic loops of bowel may obscure the diagnosis. A barium study with colonic follow through establishes the extraluminal location of the abnormal gas collection.

Films of the abdomen depicting 5 such cases are presented. The authors believe that this appearance is at least as common as the more familiar mottled gas collection.—*Adele R. Altman, M.D.*

KINMONTH, J. B., and COX, S. J. Protein-losing enteropathy in primary lymphoedema: mesenteric lymphography and gut resection. *Brit. J. Surg.*, Aug., 1974, *61*, 589–593. (From: Department of Surgery, St. Thomas's Hospital Medical School, London SE1, England.)

Hypoproteinemia has become recognized as a possible result of widespread primary disease of the lymph system in which hypoplasia has taken place on a developmental basis. Changes are found in the bowel which give rise to protein-losing enteropathy and may on occasion be associated with increased loss of fat and calcium. Investigation by mesenteric lymphography and treatment by resection of some of the more affected areas of the gut have been used as a therapeutic modality on an elective basis in the patients described in this paper. All 3 patients improved after undergoing this type of surgery.

The 3 patients are described in detail and a tabular summary reveals that the most common symptoms were edema of the legs and genitalia associated with diarrhea and on one occasion tetany. Protein loss was due to exudation and this was confirmed with the introduction of radioactively tagged protein. The lymph collects in the bowel wall and then exudes into the peritoneal cavity or into the gut lumen. Fat absorption is impaired by the build-up of chyle in the lymph pathways and hypocalcemia results.

The 3 patients described in this paper who underwent elective resection of the more affected areas of gut seem to have improved significantly on follow-up study. The most common condition in which this is found is primary lymphedema, and this is a group in which this type of abnormality has not been clearly recognized in the past.—*R. P. Andrews, M.D.*

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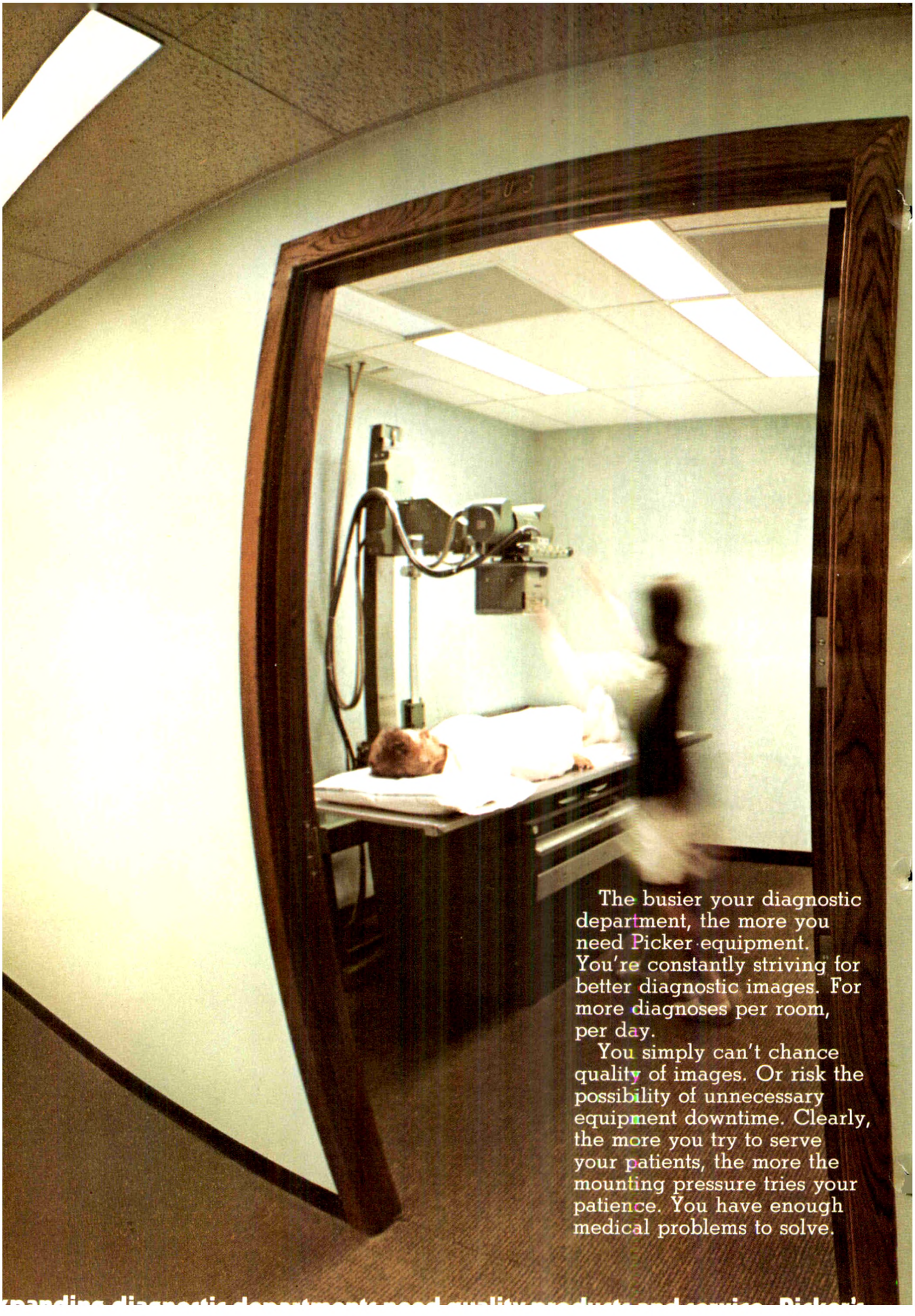

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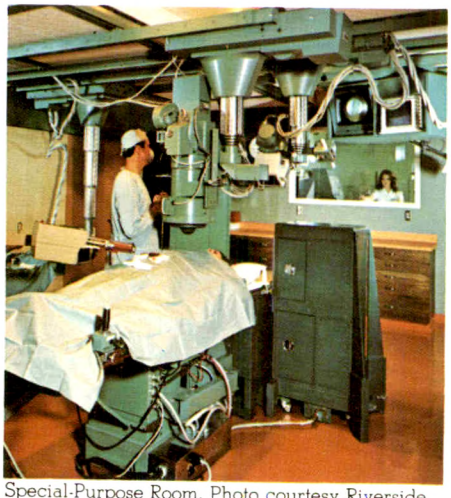

Special-Purpose Room. Photo courtesy Riverside Community Hospital, Riverside, California.

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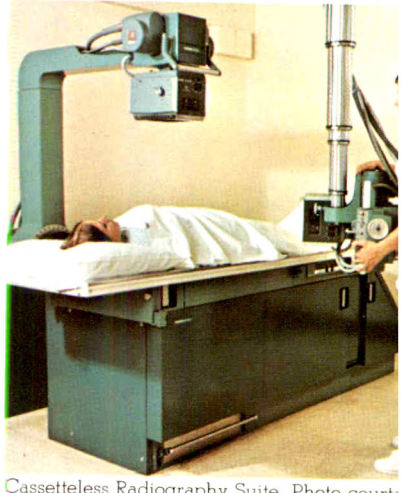
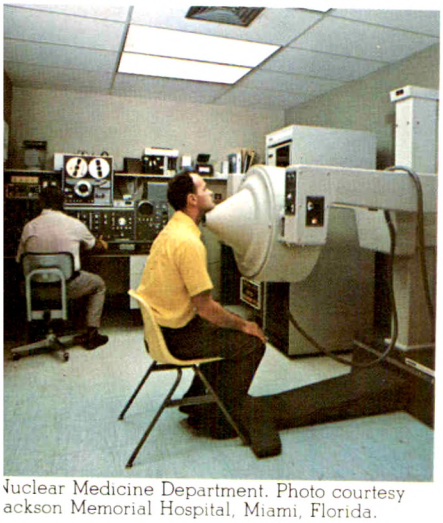
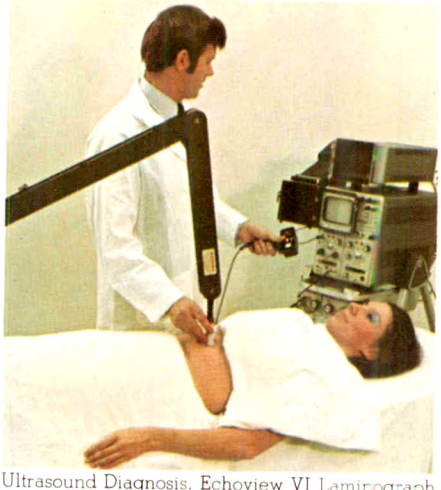


Cassetteless Radiography Suite. Photo courte Holy Family Hospital, Spokane, Washington.



Nuclear Medicine Department. Photo courtesy ackson Memorial Hospital, Miami, Florida.



Ultrasound Diagnosis. Echoview VI Laminograph being used in OB/GYN application.

Therapy Simulator Room. Photo courtesy Manitoba Cancer Institute, Winnepeg, Manitol

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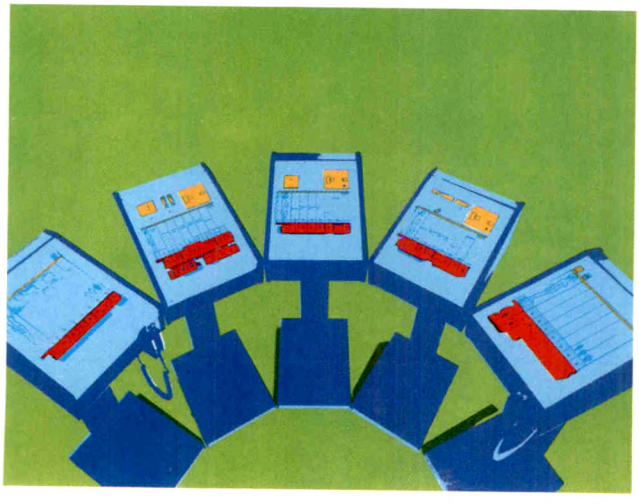

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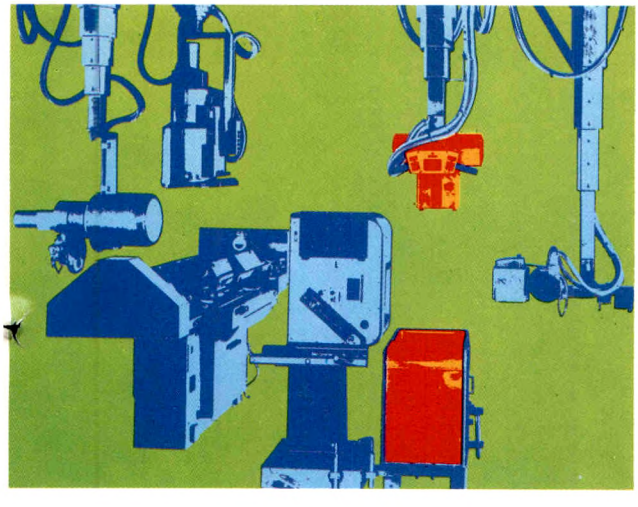

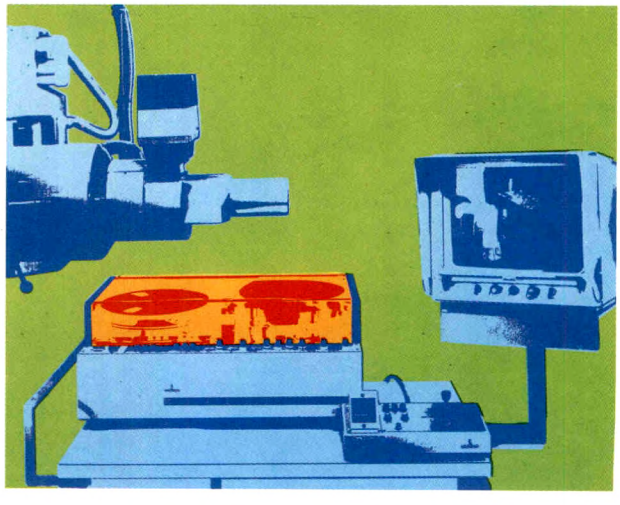

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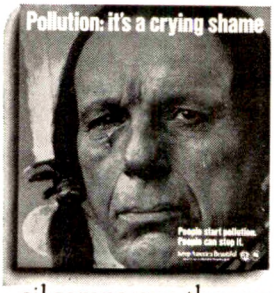

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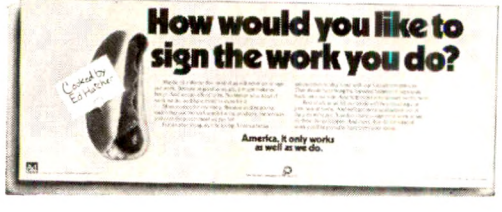
And that mark counts for a lot.



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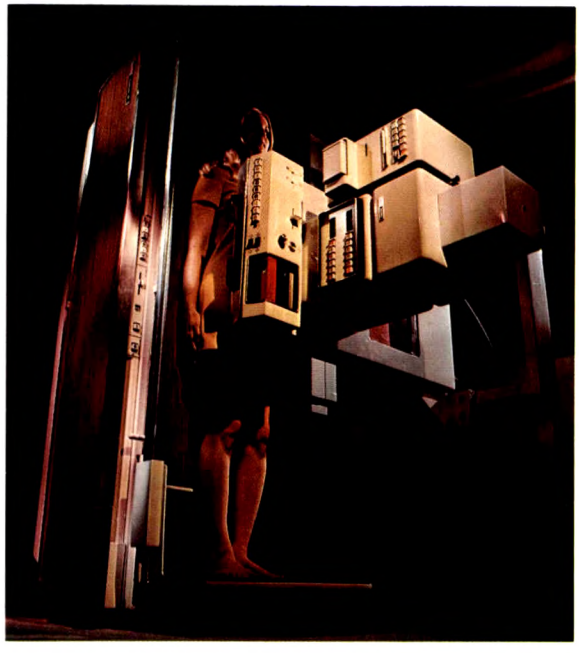

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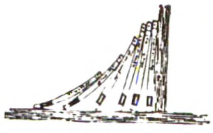

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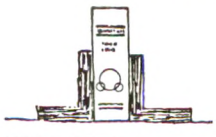

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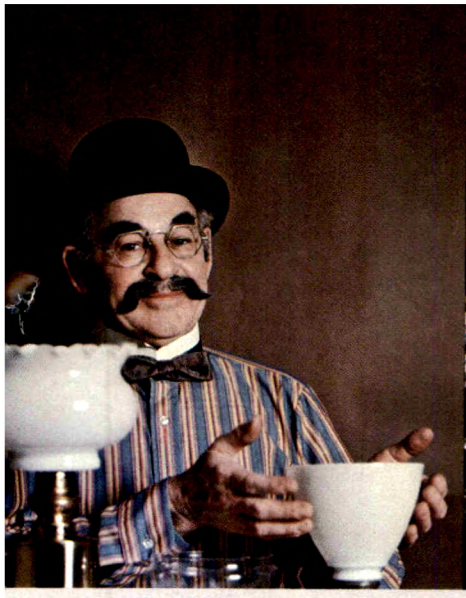

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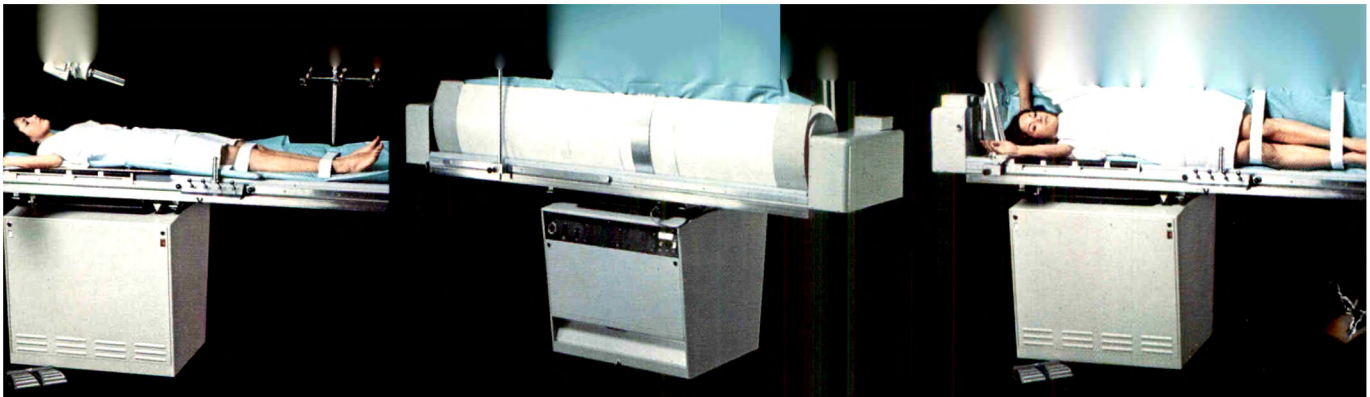

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Rotated 90° and Translated for "Gapless" Lateral Image Intensifier or Changer Studies

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"To make the best possible equipment incorporating the most sophisticated technological advancements." That's the prime objective of the Memco/Xonics alliance.

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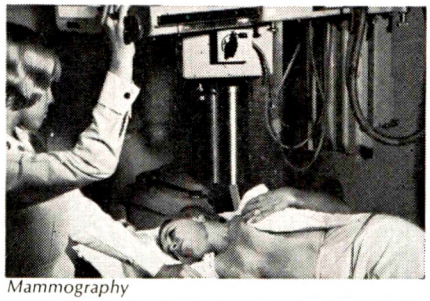
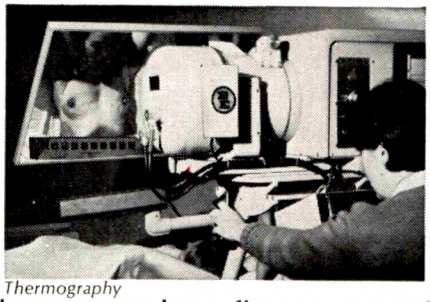
Breast Cancer: earlier warning system

Futility and frustration beset the physician confronted with breast cancer. For the last 35 years, the survival rate has not significantly changed despite intensive educational programs aimed at earlier detection, and improvement in treatment techniques.

What is the outlook? We know the key to reducing mortality from breast cancer is in the *earliest possible* diagnosis. The stage at which breast cancer is detected is *crucial* to the outcome of treatment. By the time a lump is discovered through BSE or clinical examination, critical time may have been lost.



Mammography



Thermography

And we *do* have the means to achieve earlier diagnosis. We do have an *earlier warning system.* Mammography and thermography can detect breast cancer *before* a lump is discernible by palpation. To demonstrate that it is practical and feasible to detect breast cancer earlier by using these modalities, the American Cancer Society and the National Cancer Institute are funding a network of breast cancer demonstration projects. Supported by grants of $2-million from the ACS and $4-million from the NCI, 20 such centers are expected to be operative across the country by the end of the year. Each will screen at no charge, approximately 5,000 women annually, in what is considered to be the ideal detection program — to include clinical examination, mammography and thermography. Each of these detection methods contributes independently to the detection of breast cancer, and none can be dispensed with in the search for early disease.

At present we cannot prevent breast cancer, but the potential for saving more lives is immense. The five-year survival rate changes dramatically from 53% when axillary nodes are positive, to 85% when the disease is localized, to nearly 100% for in-situ cancer.

We have an earlier warning system. Let's use it.

® american cancer society

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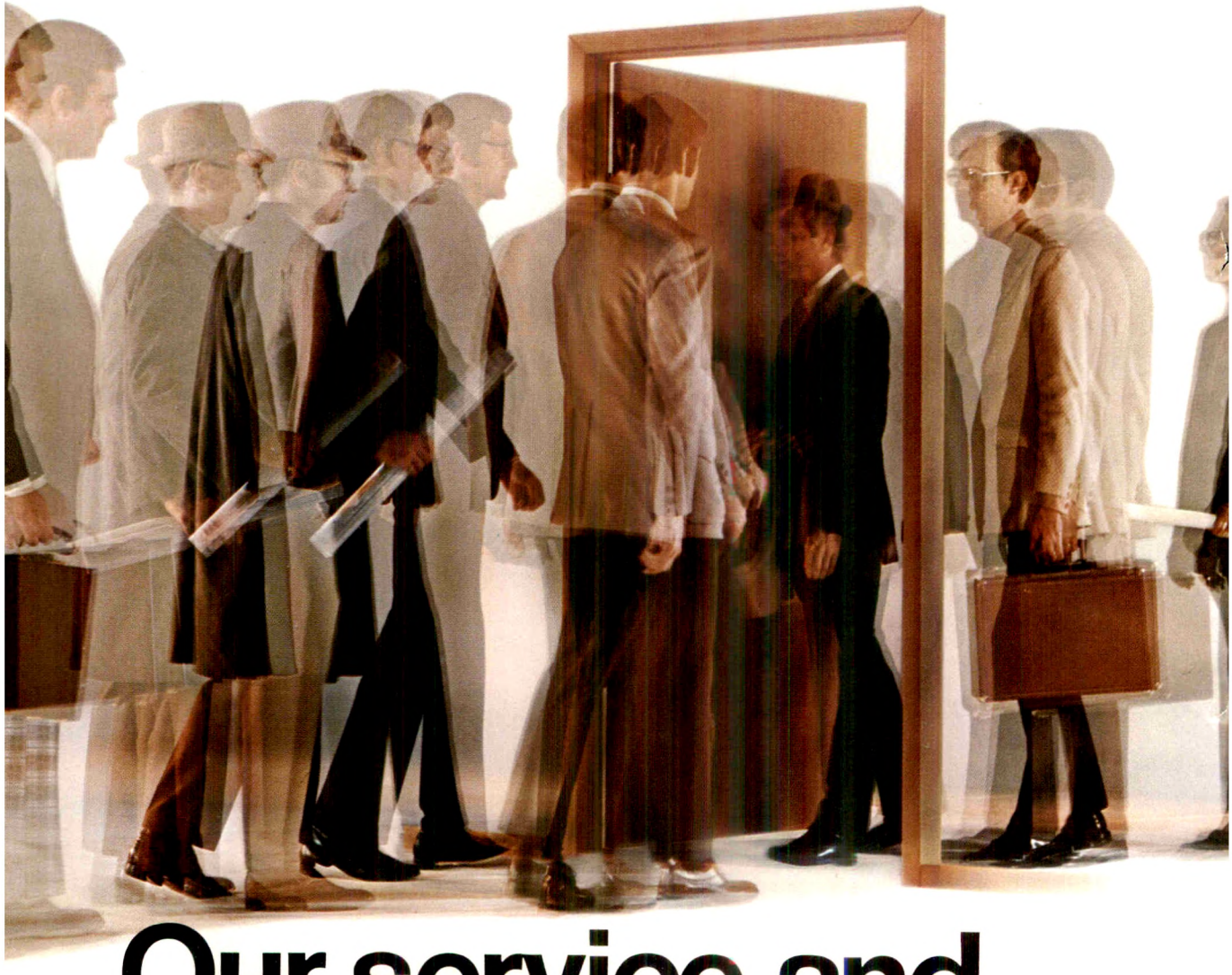

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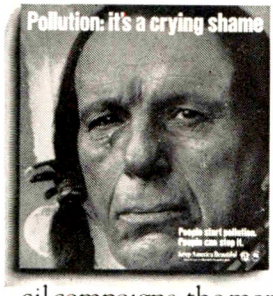

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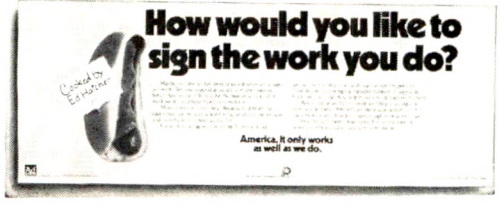

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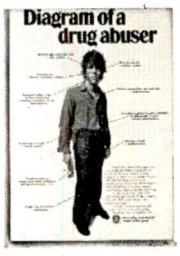

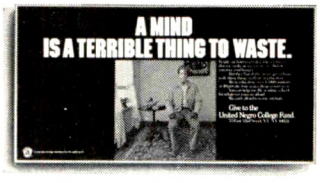

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And that mark counts for a lot.

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Benign Breast Lesions: Punctate Calcifications

"All that glisters is not gold"—Shakespeare. Which should remind the uninitiated that one cannot depend upon the *roentgen characteristics of breast calcifications alone* to diagnose or exclude malignant breast disease. Witness the following, all proved benign breast lesions considered "cancer" by mammography.

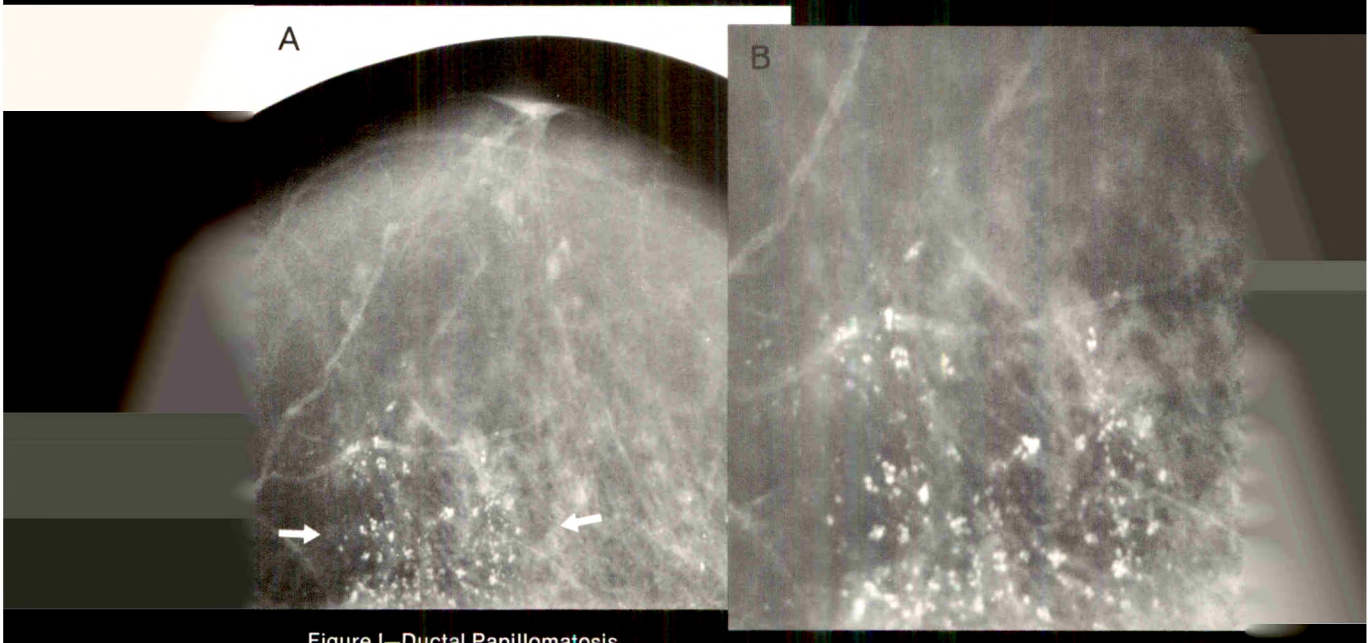

Figure I—Ductal Papillomatosis
A. Craniocaudal view reveals calcifications of varying size and configuration (arrows), seen to better advantage in Figure B, which look very much like the calcification seen in breast cancer. Clinically, the patient had no complaints. The breast was operated upon because of the mammographic suggestion of possible intraductal carcinoma. Biopsy revealed fibrocystic disease with proliferative changes including papillomatosis and adenosis.

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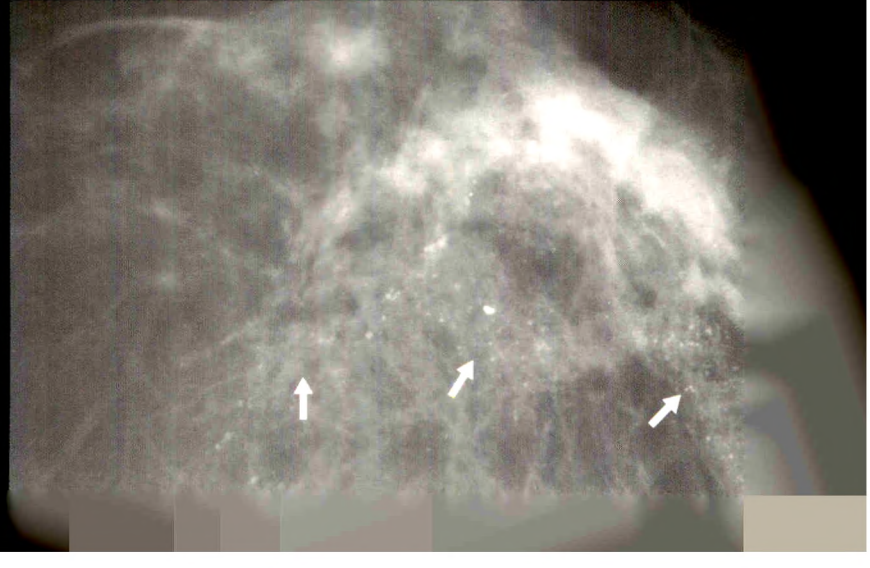

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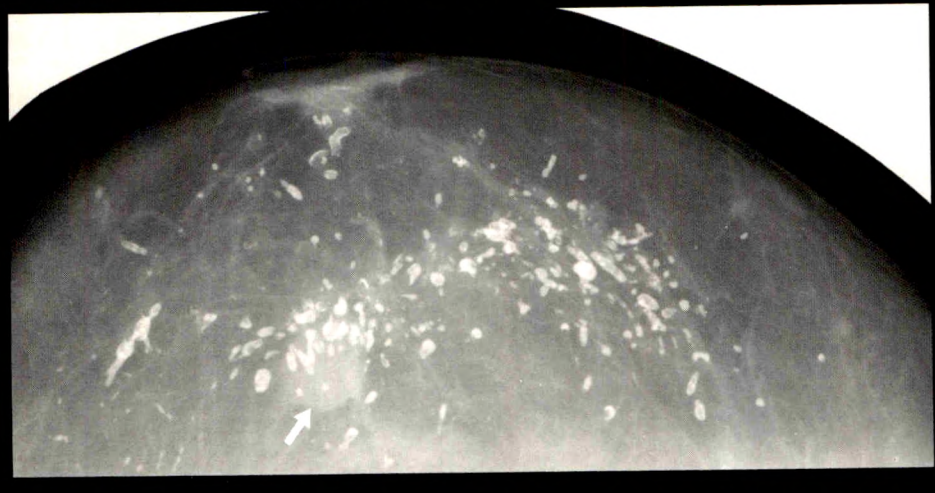
Figure III—
Fibrocystic Disease
Craniocaudal view reveals innumerable small punctate calcifications (arrows) irregular in size and outline, which suggested breast cancer by mammography. When biopsied, the patient proved to have localized fibrocystic disease with numerous foci of intraducta calcification.

Figure IV—Comedomastitis Plus Carcinoma
Craniocaudal view reveals innumerable coarse linear and somewhat round calcifications distributed throughout most of the breast. The patient was known to have a small palpable mass in the center of this breast. On close inspection, a modular density may be seen (arrow), which is partially obscured by the benign calcifications that surround it. The nodule proved to be a small (1.5 cm) carcinoma; the rest of the breast revealed extensive mammary duct ectasia with calcifications in the wall of the ducts. The experienced observer remembers that sclerosing adenosis, ductal papillomatosis, and fibrocystic disease may reveal tiny punctate calcifications that mimic cancer.



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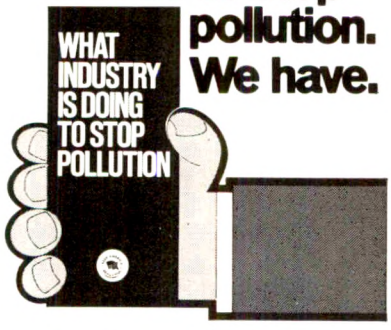

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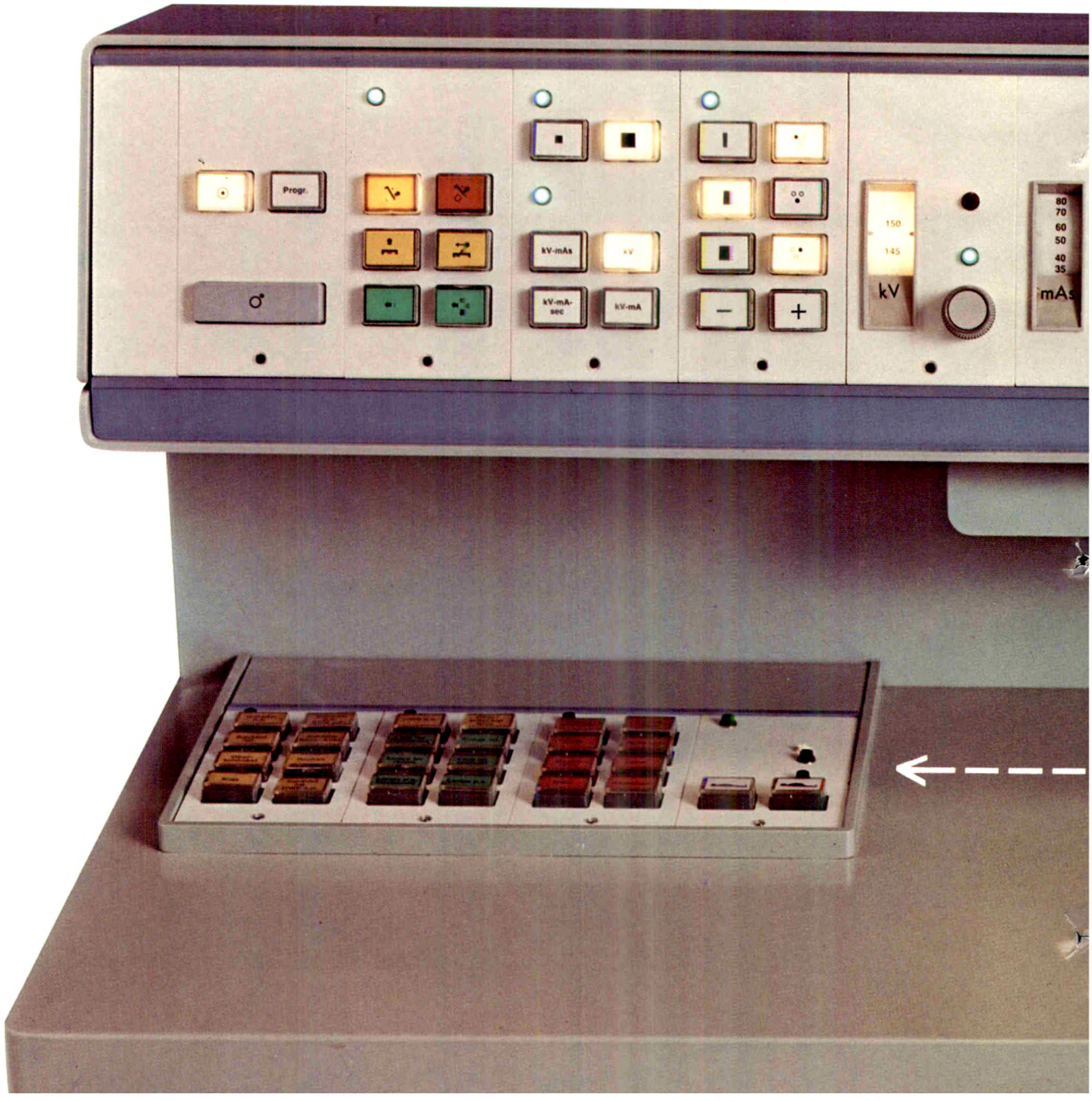

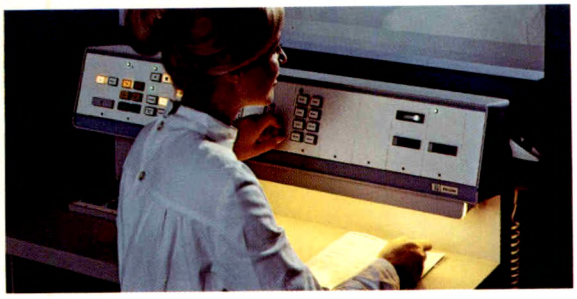

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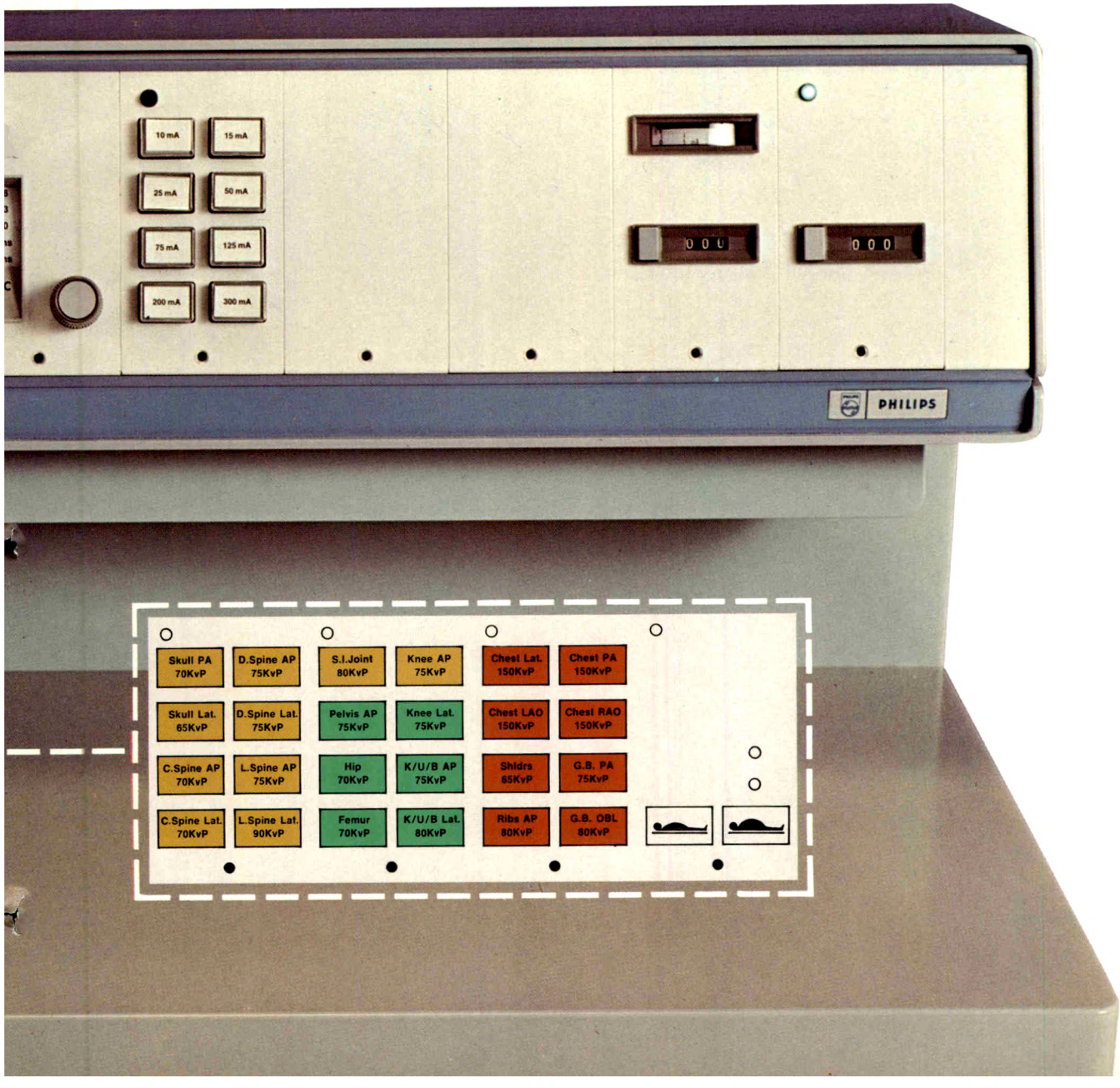

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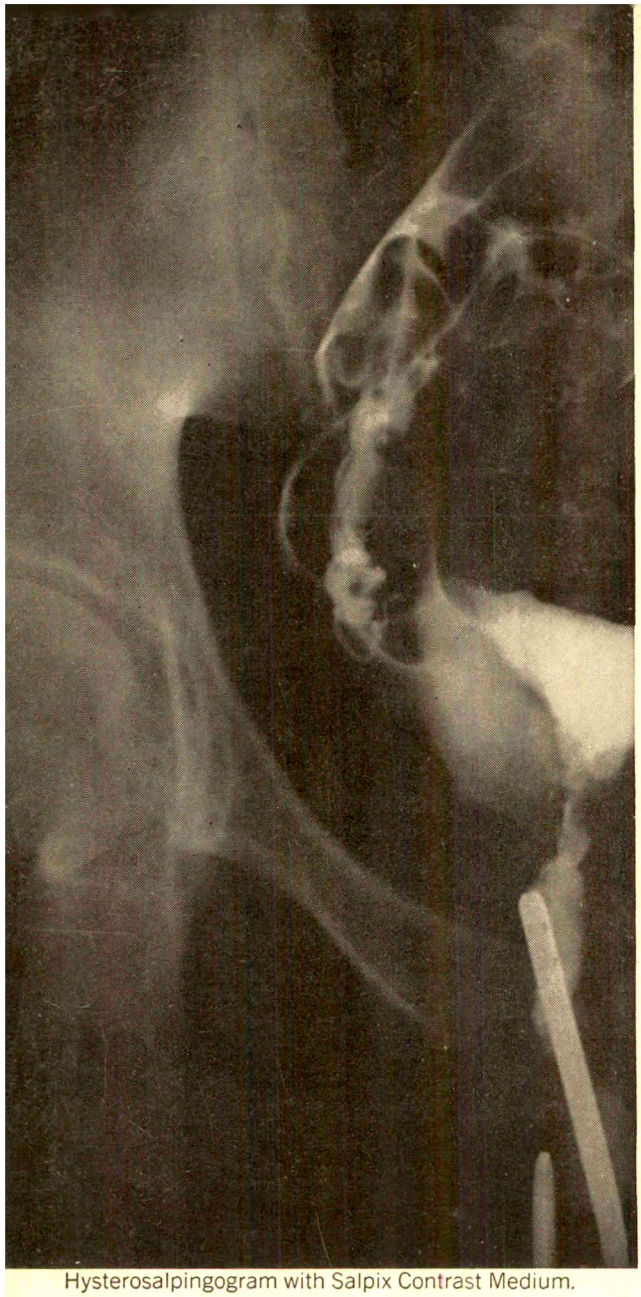

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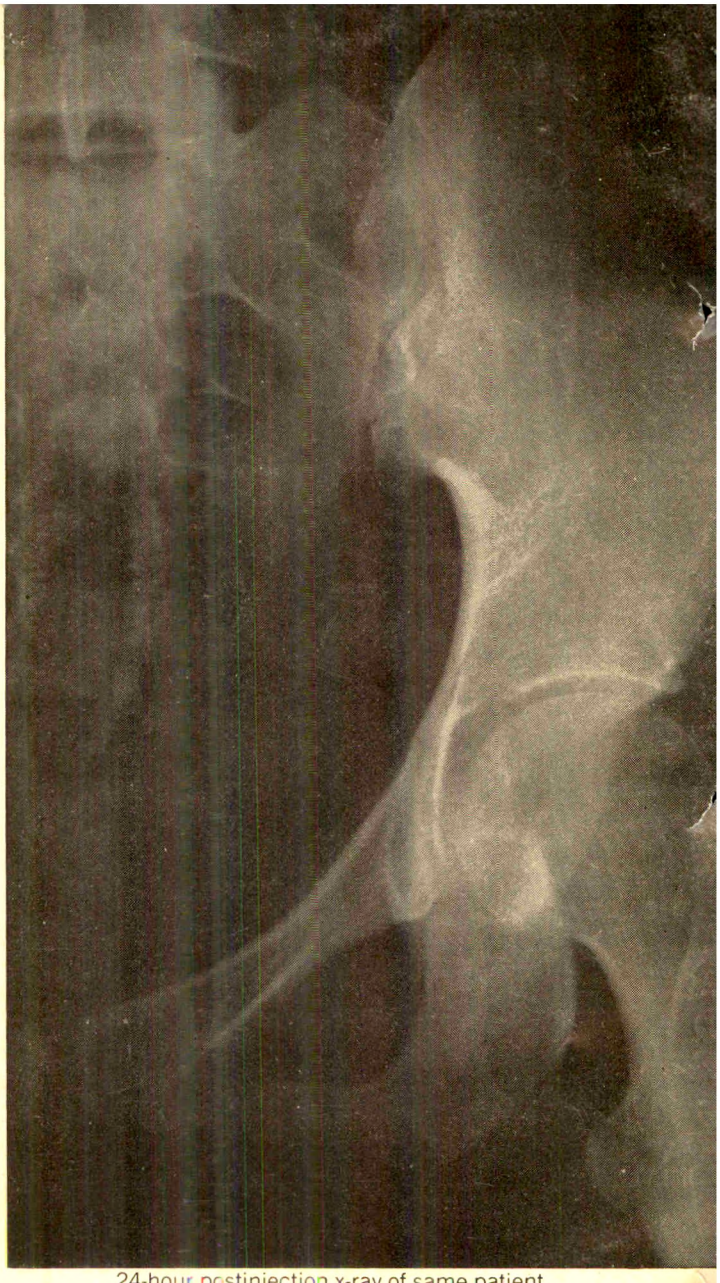

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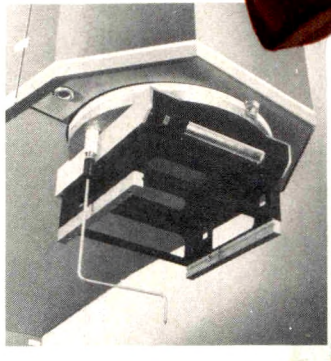

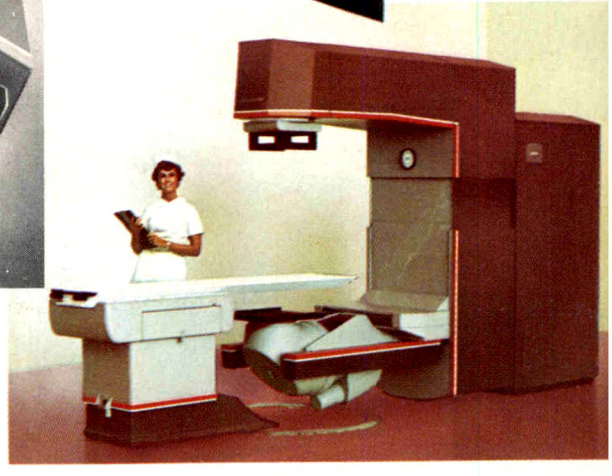

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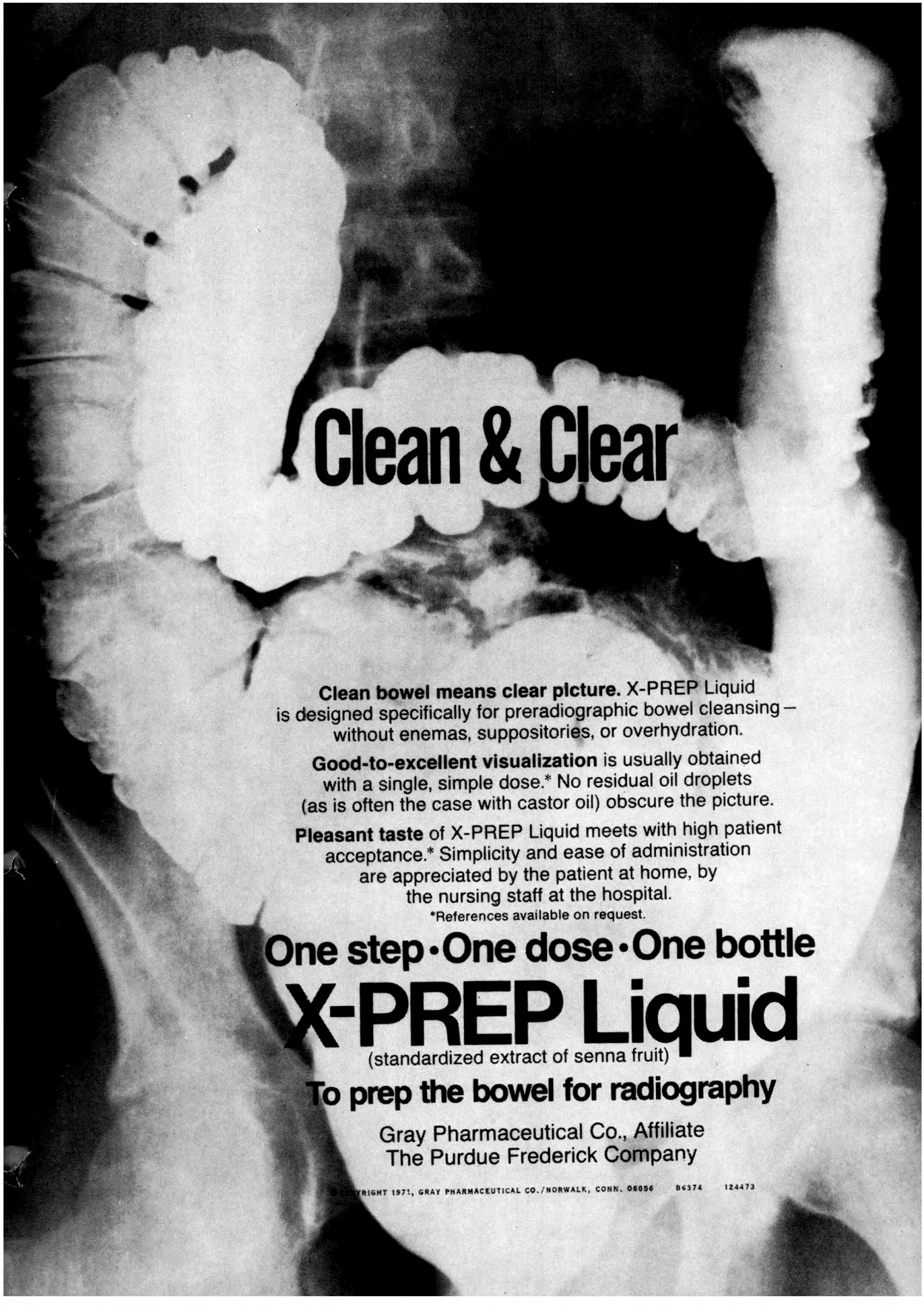

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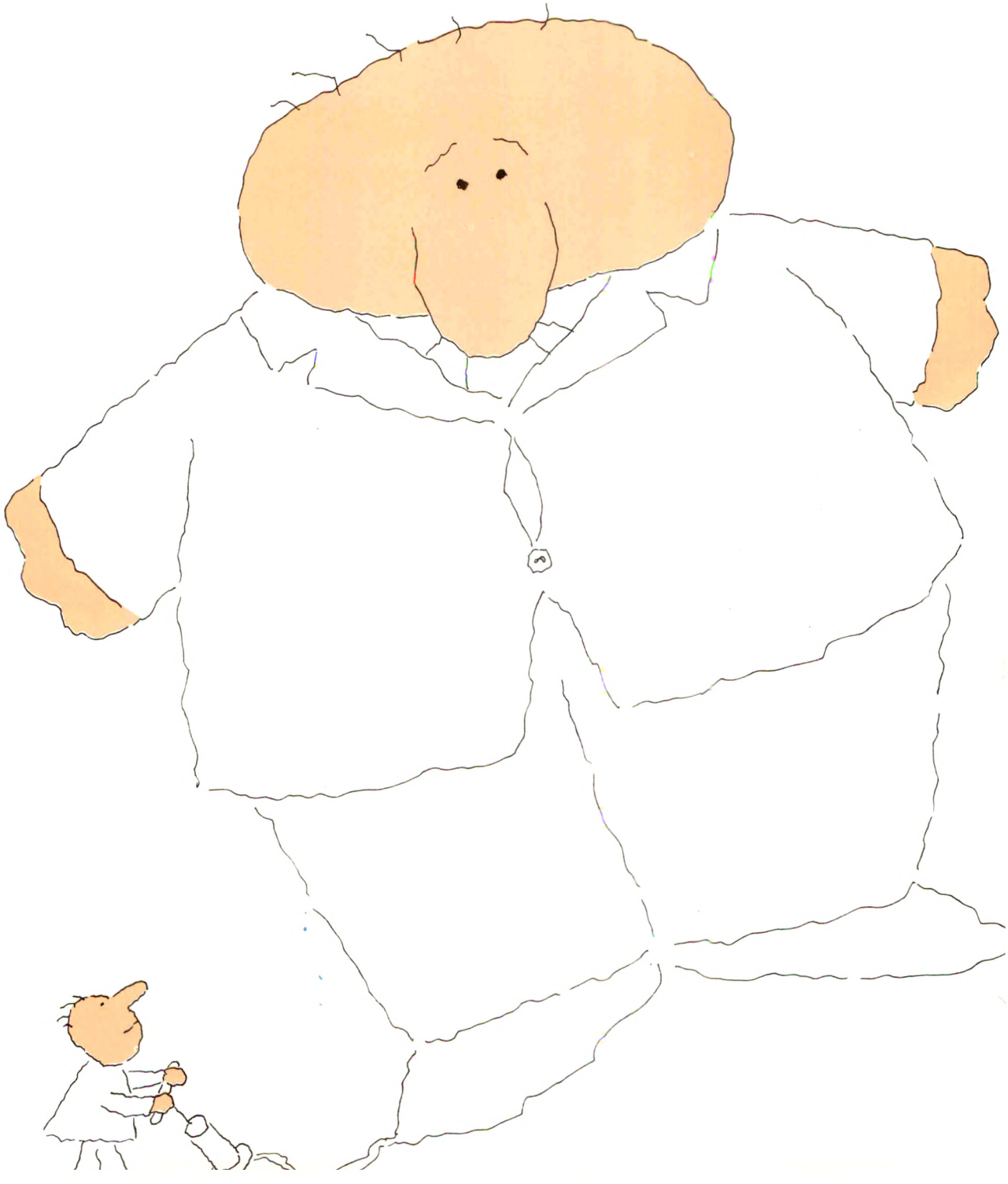

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We've hired additional people in manufacturing, R&D, customer service and most important, we've hired more technically-skilled Ilford Men and Women to help you get the most from your equipment and our materials.

Next time you see your Ilford Man, ask him about Ilford's expanded line of films for general radiography, our new family of cine films, our intensifying screens and chemicals and our quality control monitor system.

His chest may swell up a bit, but his head never will. He's just not the type.

Ilford Inc., A Ciba-Geigy Co., West 70 Century Road, Paramus, New Jersey 07652.

ILFORD

When you invest in a Philips RT 305 Unit, that's not all you're buying.

The Philips Integrated Therapy Programme ensures increased efficiency in the modern radiotherapy department by having a common design philosophy, similarity of operational procedures and simplified service.

The programme embodies maximum reliability and patient safety. It incorporates a long-term plan, providing the clinic and hospital with essential equipment for today and the future.

Equipment like the RT305. A unit that offers a new approach to X-ray therapy.

RT 305. The optimum equipment for intermediate X-ray therapy.

When normal ortho-voltage techniques requiring a lower voltage are used for irradiation of certain regions below the skin, there is an increased risk of serious skin damage and high bone absorption.

This is why Philips developed a special fixed-voltage unit: the RT305. It operates at 300kV which, in combination with extremely high filtration, ensures optimum radiation quality. The focus-skin-distance can be varied over a wide range to ensure the required depth effect in the intermediate region.

For these reasons, fixed-voltage becomes a positive advantage rather than a limitation. The ideal depth effect is obtained, simply by selecting the appropriate applicator.

The unique design of the tube housing, and the highly manoeuvrable ceiling suspension, ensure maximum ease of positioning.

Safety first.

As with all equipment in the Philips Integrated Therapy Programme, safety was of prime importance when we designed and developed the RT305 unit.

This is ensured by filters being permanently housed in the applicators. The correct filter corresponding to the right applicator.

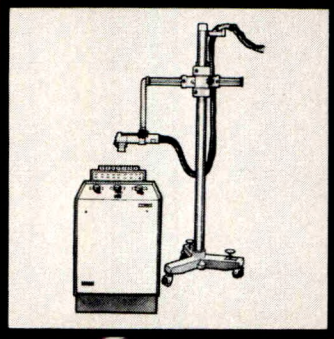
A further safety cut-out circuit is incorporated in the RT305 that makes irradiation impossible if the applicator is not fitted to the tube housing.

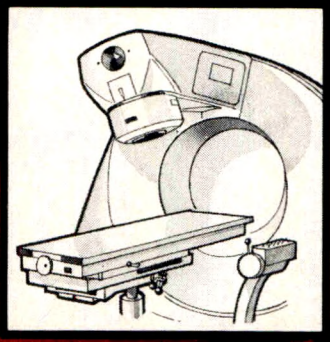
With Philips, you're planning for the future.

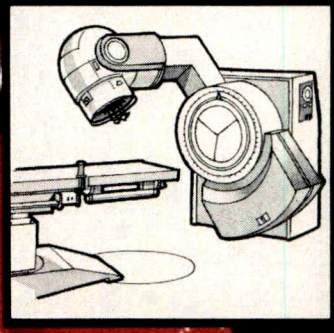
There is an entire RT range of ortho-voltage equipment. And it reflects the Philips philosophy of supplying the radiotherapy departments with the equipment they need today and meeting the demands they will make in the future.

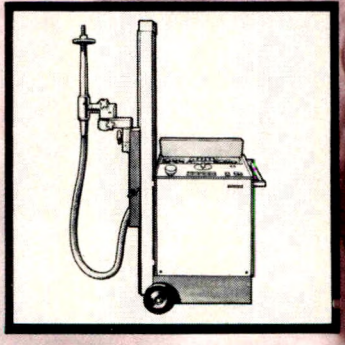
The Philips Integrated Therapy Programme includes the series of SL75 linear accelerators, cobalt units, betatrons, treatment planning system and localiser/simulator.

If you would like to know more about the Philips Integrated Therapy Programme, please write to: N.V. Philips, Medical Systems, Eindhoven, The Netherlands, or The M.E.L. Equipment Company Ltd., P.A.D. Manor Royal, Crawley, Sussex, England, or Philips Medical Systems Inc. P.O. Box 848 710 Bridgeport Avenue Shelton [illegible] 06484 U.S.A.









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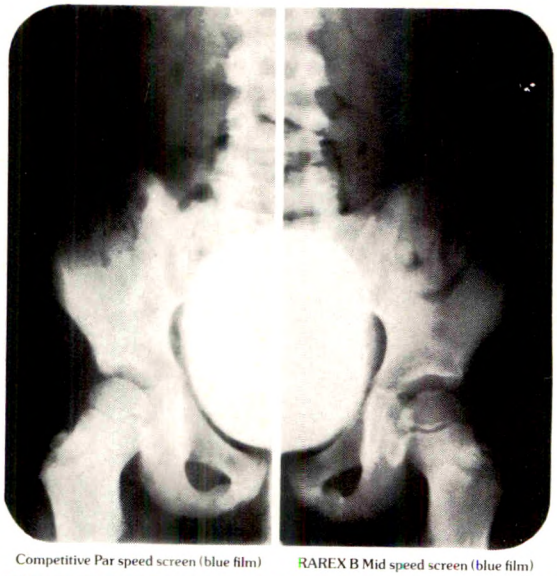

Competitive Par speed screen (blue film) RAREX B Mid speed screen (blue film)

Look what* RAREX Rare Earth Intensifying Screens *offer you:

- Greatly reduced exposure time
- Now use standard blue film
  (or orthochromatic when available)
- Improved control of motion unsharpness
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- Keep the processing system you know

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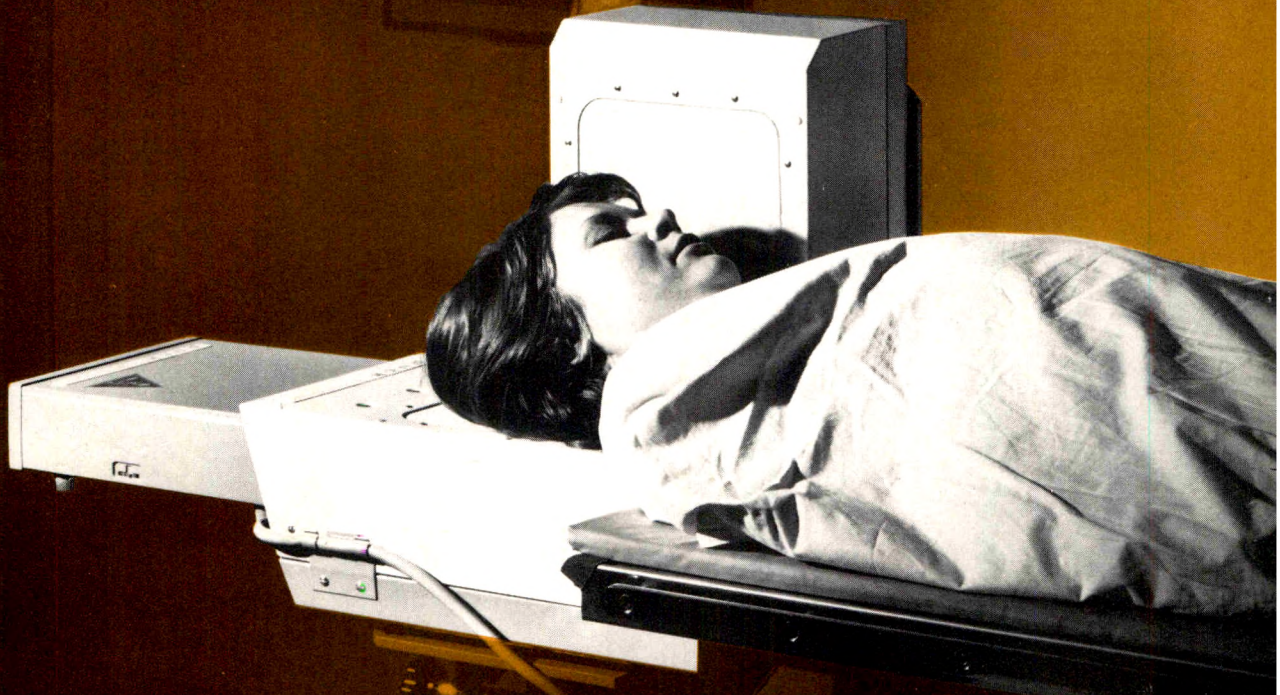

BASIC FEATURES:

- 3 exposures per second
- Biplane—*simultaneous or alternate exposures*
- 20 films capacity
- Punch card control
- Stands for various applications

3 MODELS:

U-35 film size 14″ x 14″ for abdominal, peripheral, thoracic and cerebral angiography, incl. magnification technique.

L-35 film size 14″ x 14″ has "see-through" capability for exposure monitoring on TV.

U-24 film size 24 x 30 cm (abt. 9½″ x 11¾″) fine detail, film-saving changer, especially suited for cerebral angiography.

For further information, contact your local supplier or write:

'HAT'S
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S QUIBB?

)n the current nuclear medicine scene

IINITEC® (Technetium 99m) Generator

ıe Technetium 99m Generator using fission product molybdenum to produce :chnetium 99m. MINITEC is unlike any generator you've ever used—made nall to make sense.

esigned for easy handling

- MINITEC has its own handle for easy lifting, easy carrying and reduced hand exposure
- Weighs only 24½ lbs., less than 5" in diameter, under 8½" high

esigned for easy elution

- Sets up in seconds
- Elutes in only 3 minutes after eluent vial has emptied

esigned for safety

- No exposed tubing when eluting
- 1⅝" lead surrounds the MINITEC column
- 1½" of extra lead protection from MAXI-SHIELD™. Base, cap and interlocking half rings easily assembled on site . . . only the cap is removed for elution. (You get MAXI-SHIELD free with your first MINITEC Generator purchase.)

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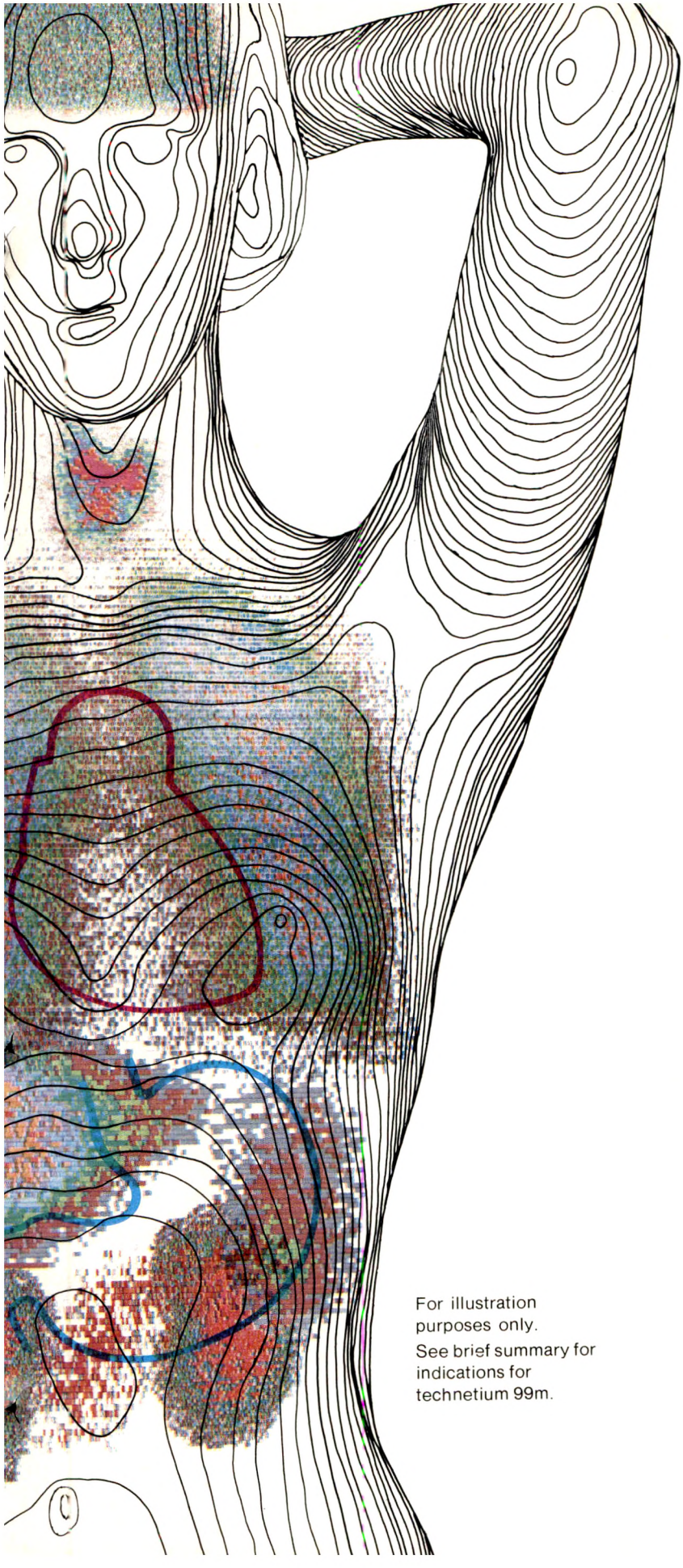
- MINITEC Generator is available in 50,100, 200, 300, 400 and 500 mCi potencies. Delivery on Monday AM (precalibrated through Thursday) and Wednesday (precalibrated through Monday) provides maximum versatility to satisfy technetium requirements of your lab's work load.



For illustration purposes only.

See brief summary for indications for technetium 99m.

Minitec®
(Technetium 99m)
Generator

Minitec® (Technetium 99m) Generator provides means of obtaining a sterile, non-pyrogenic supp of technetium 99m (^{99m}Tc) as sodium pertechneta ^{99m}Tc.

Indications: Sodium pertechnetate^{99m}Tc is indicate for brain imaging, thyroid imaging, salivary glar imaging, blood pool imaging, and placenta loca ization.

Contraindications: At present, there are no knov contraindications to the use of sodium pertechn tate ^{99m}Tc.

Warnings: Radiopharmaceuticals should be use only by physicians who are qualified by specif training in the safe use and safe handling of radi nuclides, produced by nuclear reactor or cyclotro and whose experience and training have been a proved by the appropriate federal or state agenc authorized to license the use of radionuclide

This radiopharmaceutical should not be admi istered to women who are pregnant or who ma become pregnant or during lactation unless the i formation to be obtained outweighs the possib potential risks from the radiation exposure involve Ideally, examinations using radiopharmaceutical especially those elective in nature, of a woman childbearing capability should be performed durir the first few (approximately 10) days following th onset of menses.

Since radioactive pertechnetate is secreted milk during lactation, formula-feedings should b substituted for breast-feedings.

Important: Since material obtained from the ge erator may be intended for intravenous admini tration, aseptic technique must be strictly observe in all handling. Only the eluent provided should b used to elute the generator. Do not administer m terial eluted from the generator if there is ar evidence of foreign matter.

Precautions: As in the use of any other radioactiv material, care should be taken to insure minimu radiation exposure to the patient consistent wi proper patient management and to insure minimu radiation exposure to occupational workers.

At the time of administration, the solution shou be crystal clear.

Adverse Reactions: At present, adverse reactio have not been reported following the use of sodiu pertechnetate ^{99m}Tc.

For complete prescribing information, consu package insert.

How Supplied: Minitec (Technetium 99m) Ge erator is available in potencies of 50, 100, 20 300, 400, and 500 mCi. Supplied with the generat are vials of eluent containing 5 ml. of a steri non-pyrogenic solution of 0.9% sodium chloride water for injection. Also supplied is suitable equi ment for eluting, collecting, and assaying th technetium 99m.

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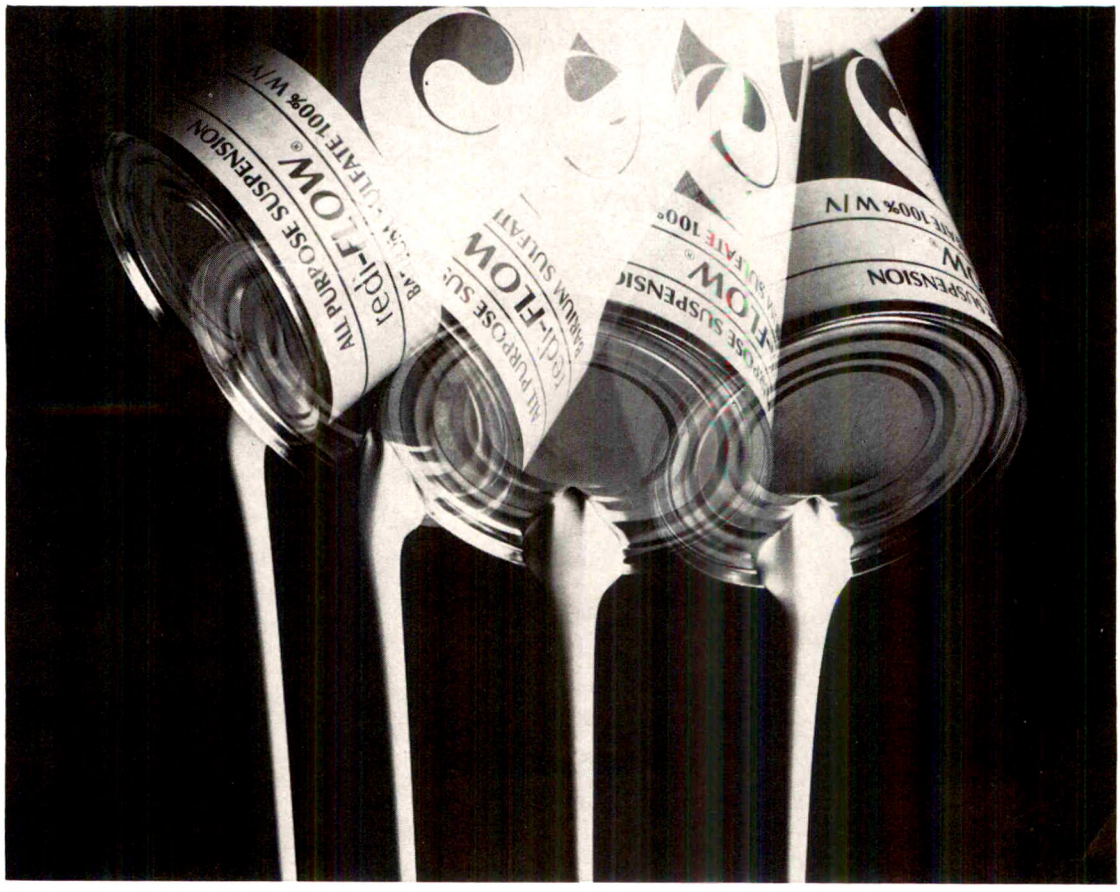

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Now—a presuspended, prehydrated barium preparation that's easy and economical to use in all gastrointestinal radiological studies:

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Time-saving redi-Flow is flavored, concentrated, prehydrated, autoclaved, and homogenized.

Ready to use—with simple dilution directions for each type of study (no blender needed).

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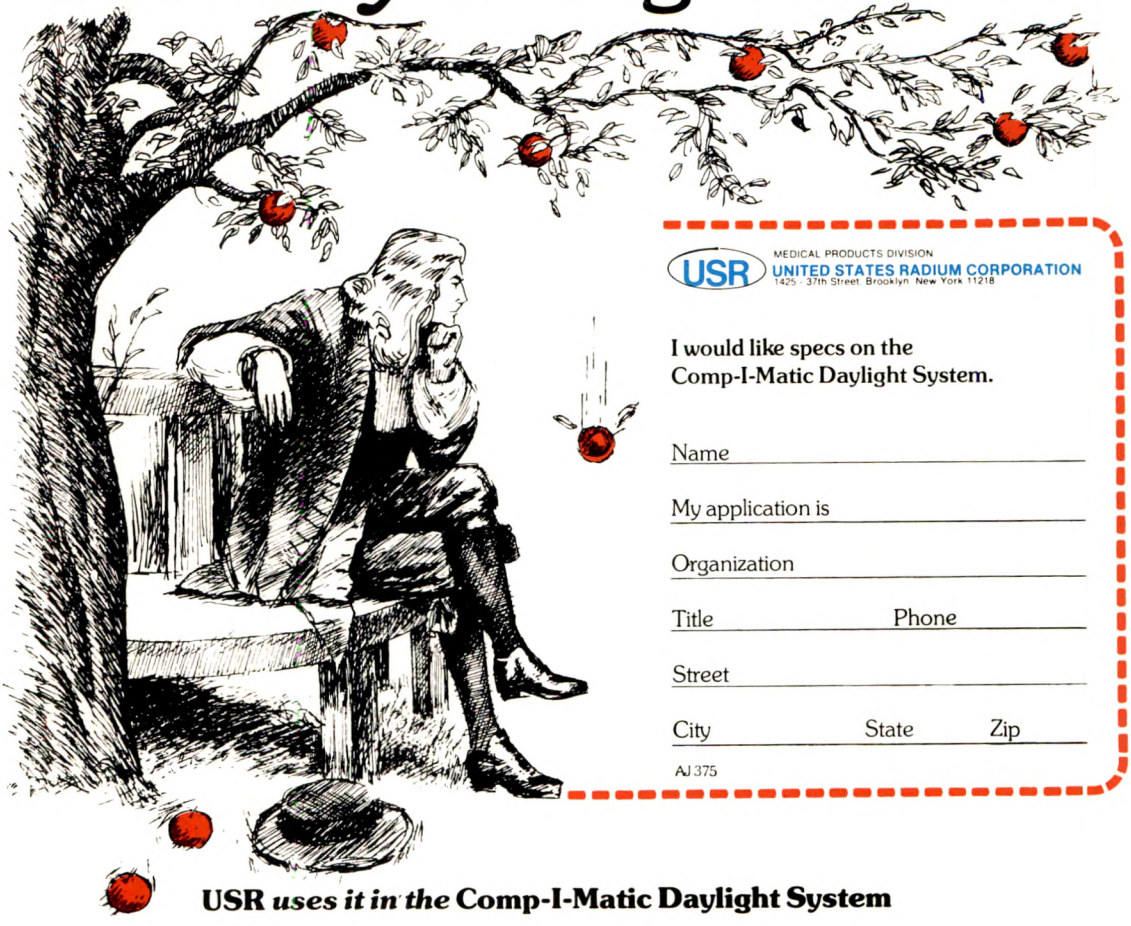

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Gravity is dependable. The new Comp-I-Matic Daylight System is designed to utilize gravity feed for reliable loading and unloading of the USR Comp-I-Sette I.

In loading, each film is picked up by vacuum, then dropped into place with minimum contact between film and intensifying screen. This eliminates static charge on film and abrasion of screen surfaces. You can use any non-interleaved film in Comp-I-Sette.

Unloading also is reliable because each film is positively displaced from the cassette, then dropped directly into your own processor, or, accumulated into a magazine. All this is done in daylight.

So, take advantage of gravity. Clip the above coupon, put it in a stamped addressed envelope and let it drop into the mailbox.

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Products that work together for you

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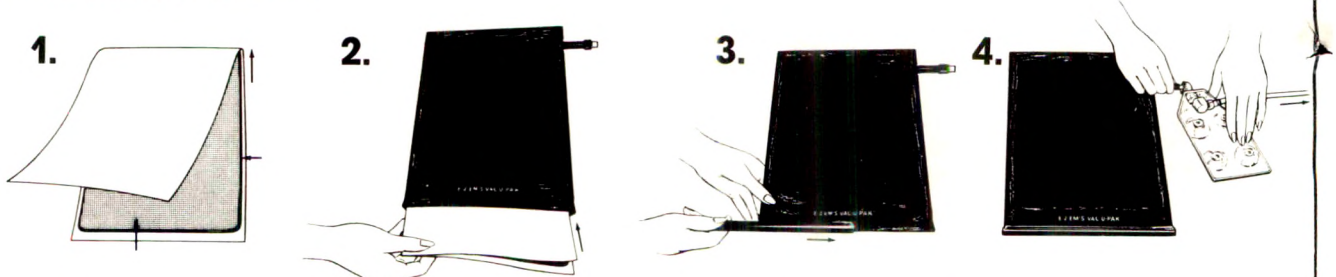
VACUPAC™

The Vacuum Cassette System for low cost, low dosage Mammography.

THE REASONS:

- Outstanding technical results (resolution in excess of 10 line pairs per millimeter)
- Greatly reduced exposures (by 85% in some instances)
- Motion unsharpness almost eliminated
- Lengthens tube life
- Simplified loading procedure
- Lightweight *reusable* cassettes
- Absolute film screen contact

THE MECHANISM:



1. Insert screen to fold.
2. Insert Lo-dose Film, emulsion side to screen.
3. Place Vac-U-Pak Cassette on table with valve in upper right hand corner.
4. Slide folder-screen-film sandwich, folded end first, into Vac-U-Pak Cassette.
5. Smooth Vac-U-Pak Cassette sliding your hand toward open end.
6. Slide rigid closure over open end.
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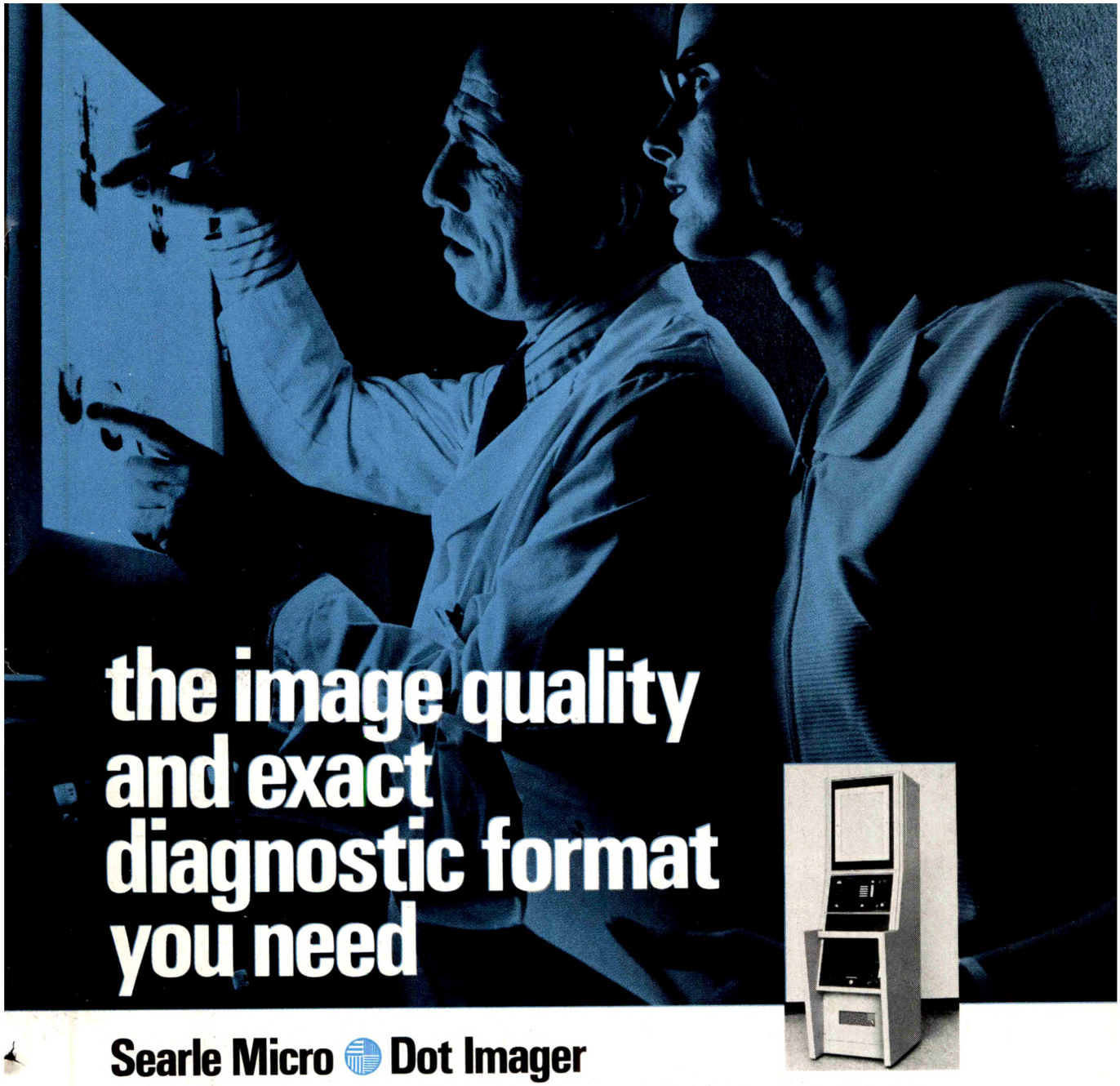

the image quality and exact diagnostic format you need

Searle Micro Dot Imager

Static, dynamic & whole body imaging . . . 15 formats, 3 film sizes

The Searle Micro Dot Imager offers Pho/Gamma users a versatile display system for single-organ or whole body imaging using economical X-ray film. Three film sizes and 15 image formats let you choose the exact format best suited for any study. State-of-the-art optics and electronics put as many as 80 images on one film with single-image fidelity. You can even mix static, dynamic and different size images on the same sheet of film. An exclusive, lightweight cassette design speeds and simplifies loading and unloading of film.

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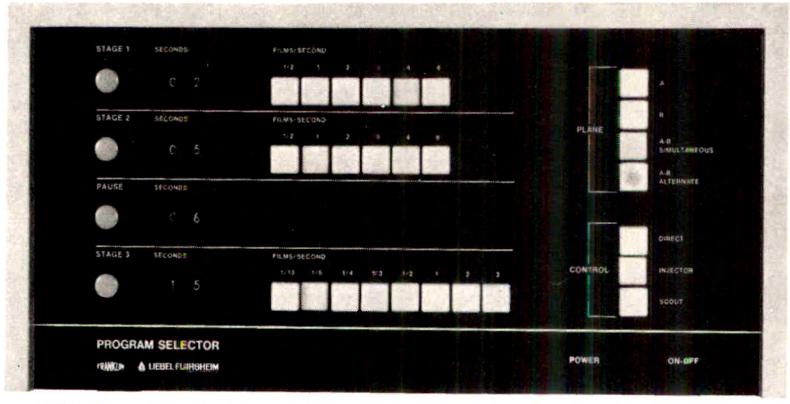
- Trouble-free printed circuits
- Integrated circuit components



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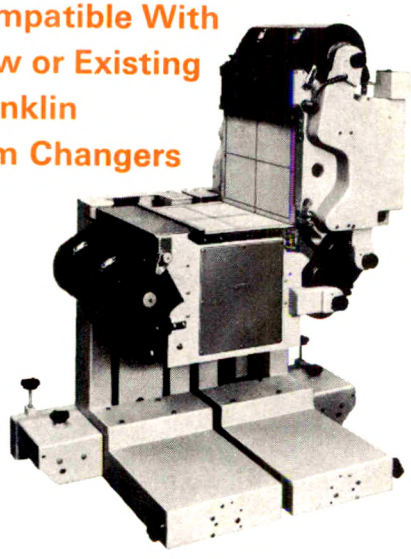

- Expanded film speeds for each stage . . . down to one film in 10 seconds on 3rd stage.
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- Separate handswitch
- Last film automatically advances into Receiver

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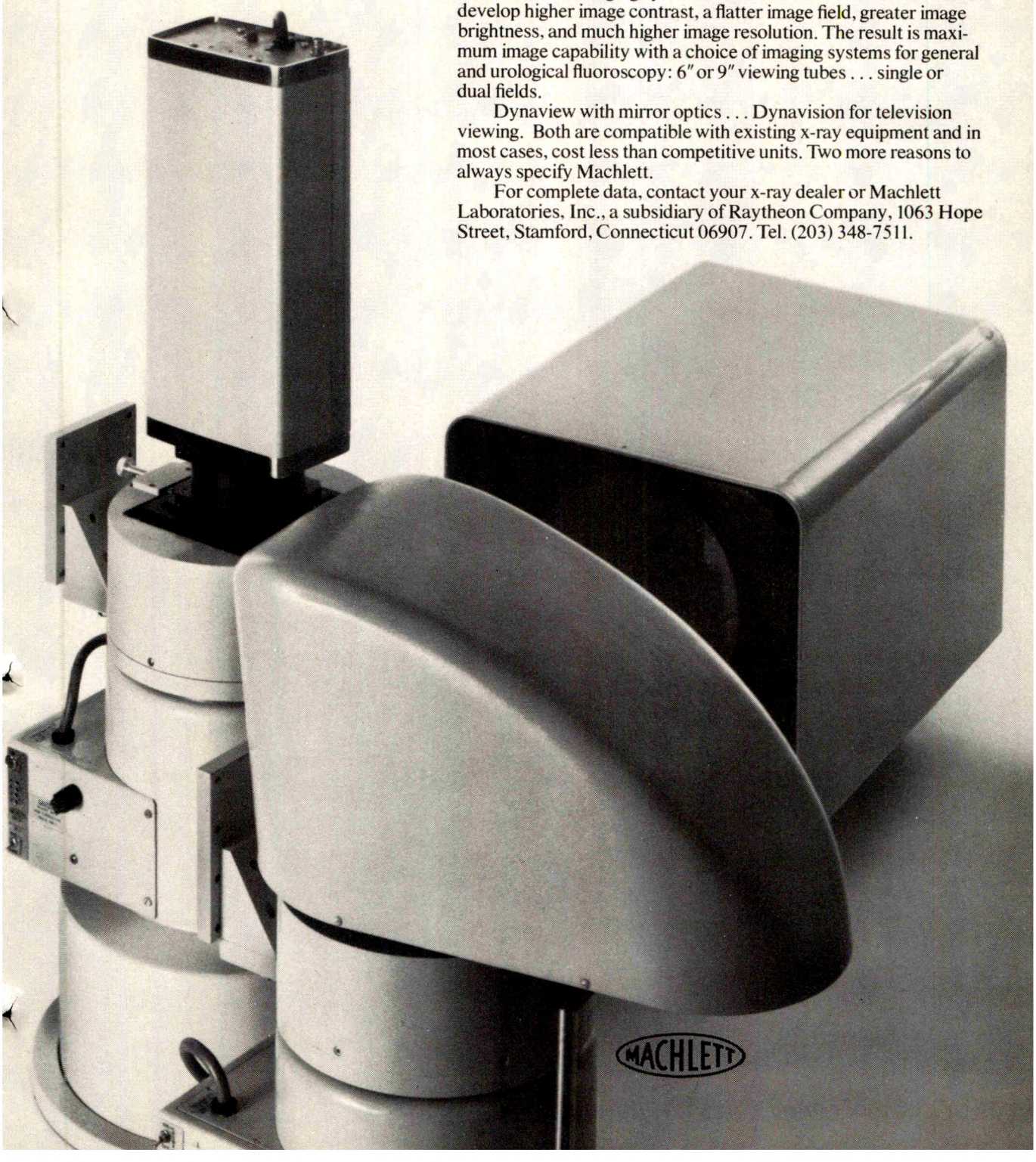
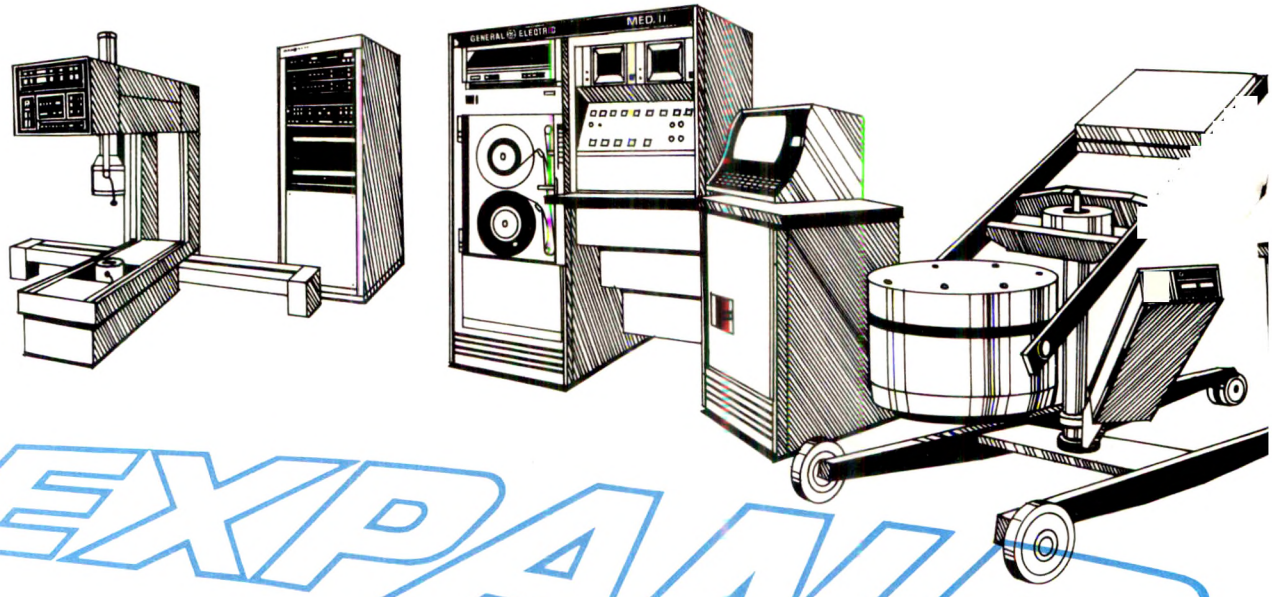
A Machlett Dynaview or Dynavision image intensification system with cesium iodide imaging tubes can easily integrate with and improve your conventional fluoroscopic equipment. Here's how: Machlett imaging systems with advanced cesium iodide tubes develop higher image contrast, a flatter image field, greater image brightness, and much higher image resolution. The result is maximum image capability with a choice of imaging systems for general and urological fluoroscopy: 6″ or 9″ viewing tubes . . . single or dual fields.

Dynaview with mirror optics . . . Dynavision for television viewing. Both are compatible with existing x-ray equipment and in most cases, cost less than competitive units. Two more reasons to always specify Machlett.

For complete data, contact your x-ray dealer or Machlett Laboratories, Inc., a subsidiary of Raytheon Company, 1063 Hope Street, Stamford, Connecticut 06907. Tel. (203) 348-7511.



What's General Electric doing in nuclear medicine?



EXPANDI

Previously, General Electric's nuclear medicine line included a Maxiscan™ 2-probe whole body scanner, and a Videodisplay processing unit. Both products are backed by a knowledgeable sales/service group, large in number, nearby when needed.

Now, to meet the growing demands of nuclear medicine, General Electric has acquired the rights to the nuclear medicine product line of Nuclear Data, Inc.

These products have a proven track record. Innovative scintillation cameras (PortaCamera, RadiCamera II) with unrivaled performance and remarkable portability. First and second generation computerized systems (Med Stor, Med II) specifically designed for nuclear medicine diagnostic tests. And ancillary equipment, such as a whole body imager attachment.

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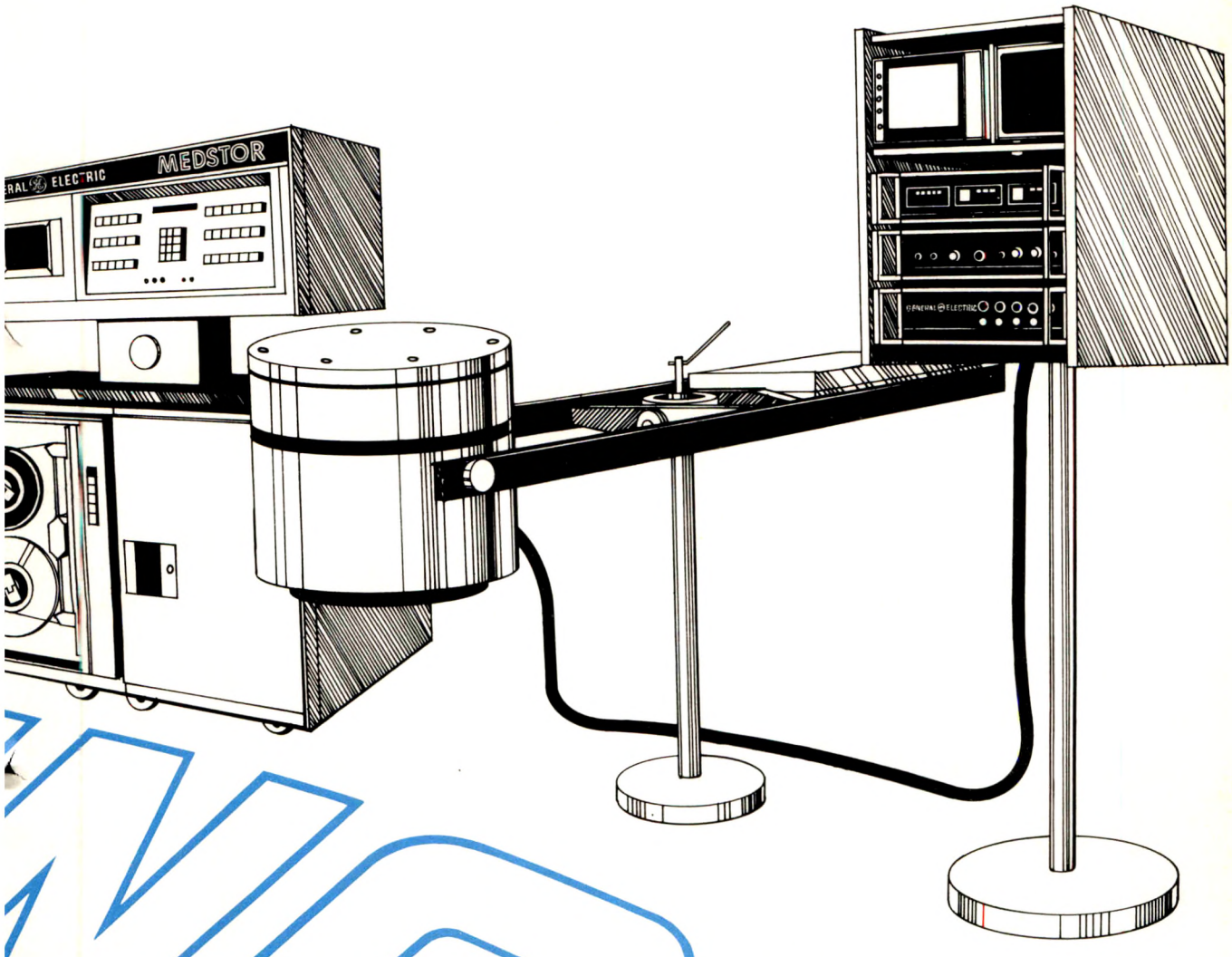

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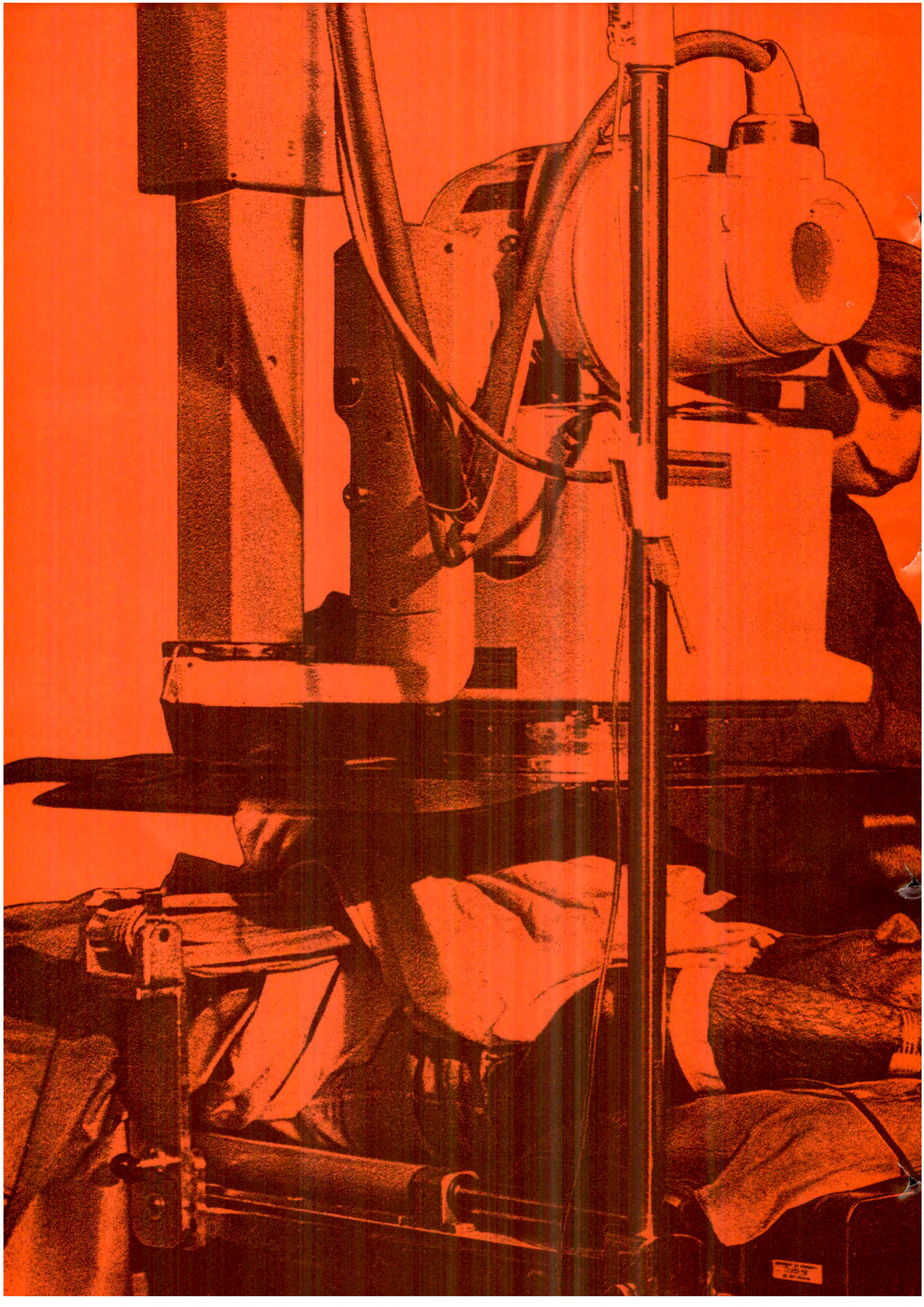

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The Trimax Rare Earth Imaging System is the fastest screen-film combination available. The syst comprises two new rare earth phosphor intensifyi screens and two specially matched medical X-ray films. The result: a two to four times increase in sp with no loss in information...ideal for special procedures.

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Trimax fits your rapid film changer. Both screens and film have been designed for optimal performa in rapid film changing equipment. Trimax films wit unique surface and antistatic properties are availa for all popular film changers.

Trimax calls for no major expenditures. In fact, it might save money by increasing the efficiency your existing equipment. We would be happy to schedule an evaluation of the Trimax System at yc convenience. Just put the coupon in the mail; you'll hear from us shortly.

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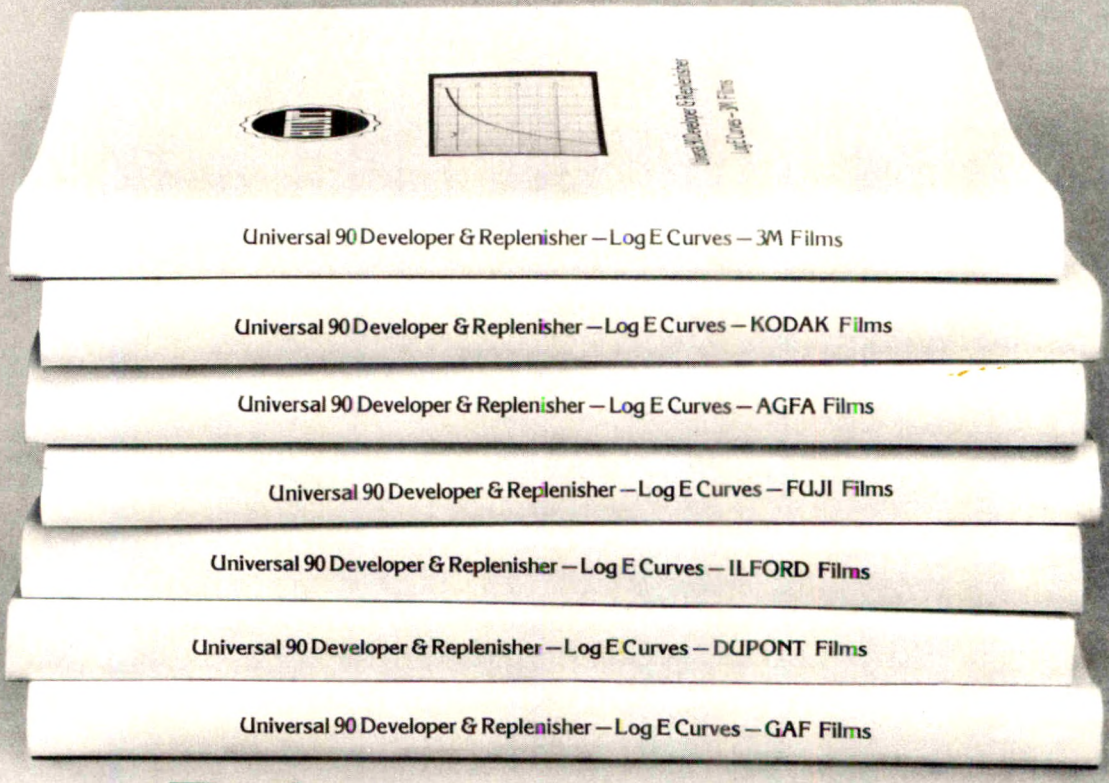

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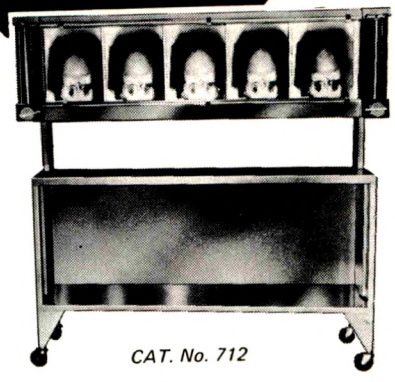
ROLL FILM VIEWER

FOR 14" WIDE FILM



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- **14" x 56" VIEWING AREA, READ 5– 11" x 14"S**
- **FILM ON REELS THE FAST, EASY WAY**
- **NYLON FILM GUIDES**
- **TILTING MOUNT ON MOBILE BASE AVAILABLE**

A new illuminator specially designed to read 14" wide films in long lengths from reels. Units feature fluorescent lighting with five 11 x 14" areas and individual control of light in each area. Film is pre-wound on a reel.

The reel is inserted into the holder and the film threaded through nylon guides onto takeup reel. Turn the handle to move the film across the viewer from reel to reel.

Illuminator can be wall mounted or ordered with its own mobile base.

Cat. No. 711: Illuminator with (2) two reels 66¾" W, 19" H 6⅛"

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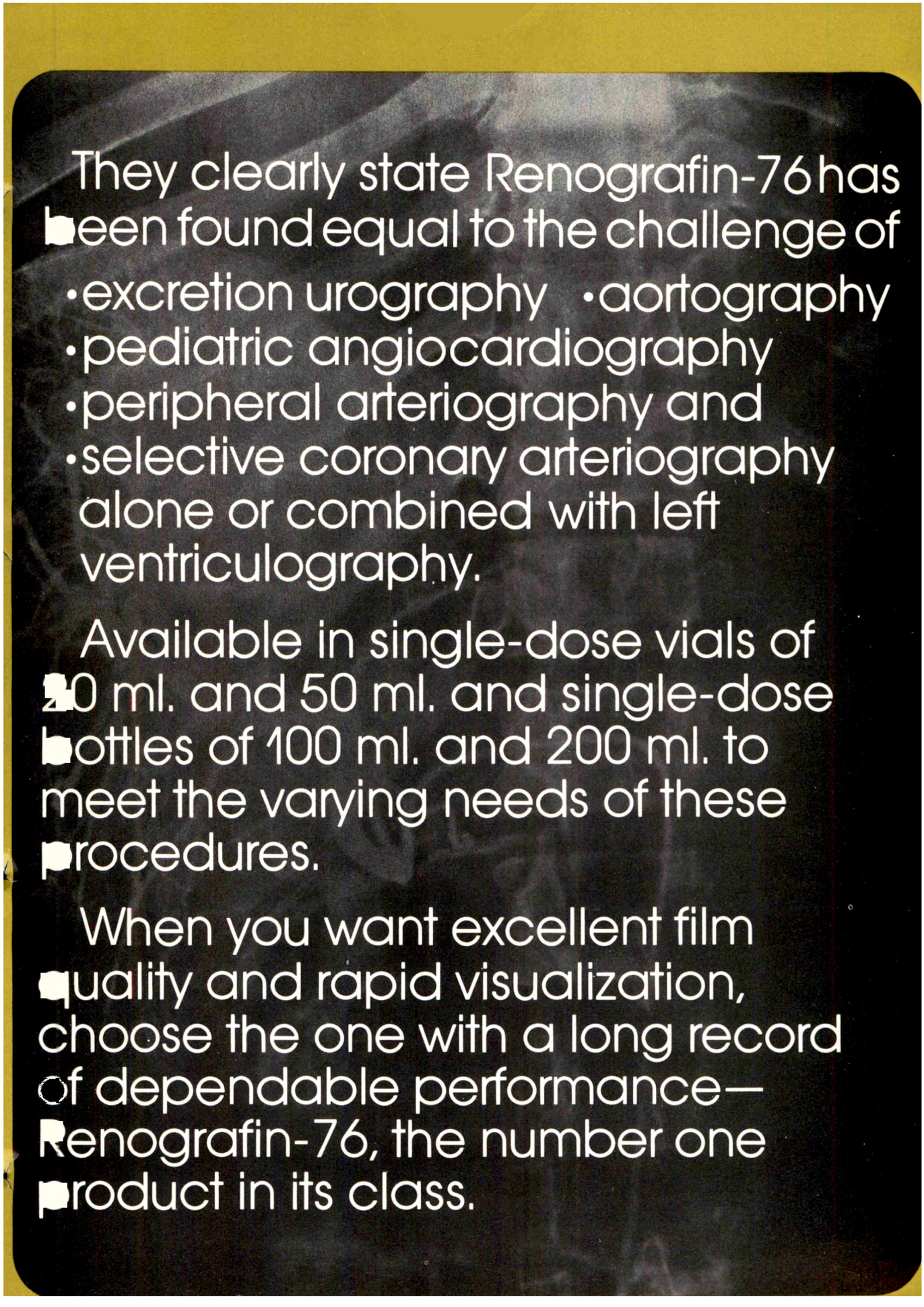
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CONTRAINDICATIONS: In patients with a hypersensitivity to salts of diatrizoic acid. Urography contraindicated in patients with anuria.

WARNINGS: A definite risk exists with the use of contrast agents in excretion urography in patients with multiple myeloma. There has been anuria with progressive uremia, renal failure and death. This risk of the procedure in these patients is not a contraindication; however, partial dehydration in preparation for study is not recommended since it may predispose for precipitation of myeloma protein in renal tubules. No therapy, including dialysis, has been successful in reversing this effect. Myeloma should be considered in persons over 40 before undertaking urographic procedures.

In cases of known or suspected pheochromocytoma, if the physician feels that the possible benefits outweigh the considered risks, radiopaque materials should be administered with extreme caution; however, an absolute minimum of material should be injected, the blood pressure should be assessed throughout the procedure, and measures for treating a hypertensive crisis should be available.

Contrast media may promote sickling in homozygous individuals when injected I.V. or intra-arterially. Although a history of sensitivity to iodine *per se* or to other contrast media is not an absolute contraindication, administration of diatrizoate requires extreme caution in such cases. Renografin-76 should be used in pregnant patients only when the physician deems its use essential to the welfare of the patient since safe use during pregnancy has not been established. Perform thyroid function tests prior to administration of Renografin-76 since iodine-containing contrast agents may alter the test results.

Weigh the inherent risks against necessity for performing *angiocardiography* in cyanotic infants and patients with chronic pulmonary emphysema. In *pediatric angiocardiography*, a dose of 10 to 20 ml. may be particularly hazardous in infants weighing less than 7 kg.; this risk is probably significantly increased if these infants have preexisting right heart "strain," right heart failure, and effectively decreased or obliterated pulmonary vascular beds. Perform *urography* with extreme caution in persons with severe concomitant hepatic and renal disease. Perform *selective coronary arteriography* only in selected patients and those in whom expected benefits outweigh the procedural risk.

PRECAUTIONS: Diagnostic procedures involving use of contrast agents should be performed under the direction of personnel with prerequisite training and a thorough knowledge of the particular procedure. Appropriate facilities should be available for coping with situations which may arise as a result of the procedure and for emergency treatment of severe reactions to the contrast agent itself; competent personnel and emergency facilities should be available for at least 30 to 60 minutes after I.V. administration since delayed reactions have been known to occur. These severe life-threatening reactions suggest hypersensitivity to the contrast agent. A personal or family history of asthma or allergy or a history of a previous reaction to a contrast agent warrants special attention and may predict more accurately than pretesting the likelihood of a reaction although not the type nor severity of the reaction in the individual. The value of any pretest is questionable. The pretest most performed is the slow I.V. injection of 0.5 to 1.0 ml. of the preparation prior to injection of the full dose; however, the absence of a reaction to the test dose does not preclude the possibility of reaction to the full diagnostic dose. Should the test dose produce an untoward response, the necessity for continuing the examination should be re-evaluated. If deemed essential, examination should proceed with all possible caution. In rare instances, reaction to the test dose may be extremely severe; therefore, close observation and facilities for emergency treatment are indicated.

Renal toxicity has been reported in a few patients with liver dysfunction who were given oral cholecystographic agents followed by urographic agents; therefore, if known or suspected hepatic or biliary disorder exists, administration of Renografin-76 should be postponed following the ingestion of cholecystographic agents. Consider the functional ability of the kidneys before injecting Renografin-76. Use cautiously in severely debilitated patients and in those with marked hypertension. Bear in mind the possibility of thrombosis when using percutaneous techniques.

In *excretion urography*, adequate visualization may be difficult or impossible in uremic patients or others with severely impaired renal function (see Contraindications). In *aortography* repeated intra-aortic injections may be hazardous; this also applies to *pediatric angiocardiography* particularly in infants weighing less than 7 kg. (see Warnings). In *peripheral arteriography*, hypotension or moderate decreases in blood pressure seem to occur frequently with intra-arterial (brachial) injections; this is transient and usually requires no treatment. Monitor blood pressure during the immediate 10 minutes after injection. It is recommended that *selective coronary arteriography* not be performed for about 4 weeks after diagnosis of myocardial infarction; mandatory prerequisites to this procedure are experienced personnel, ECG monitoring apparatus, and adequate facilities for immediate resuscitation and cardioversion.

ADVERSE REACTIONS: Nausea, vomiting, flushing, or a generalized feeling of warmth are the reactions seen most frequently with intravascular injection. Symptoms which may occur are chills, fever, sweating, headache, dizziness, pallor, weakness, severe retching and choking, wheezing, a rise or fall in blood pressure, facial or conjunctival petechiae, urticaria, pruritus, rash, and other eruptions, edema, cramps, tremors, itching, sneezing, lacrimation, etc. Antihistaminic agents may be of benefit; rarely, such reactions may be severe enough to require discontinuation of dosage. There have been a few reports of a burning or stinging sensation or numbness, of venospasm or venous pain, and of partial collapse of the injected vein. Neutropenia or thrombophlebitis may occur. Severe reactions which may require emergency measures (see Precautions) are a possibility and include cardiovascular reaction characterized by peripheral vasodilatation with hypotension and reflex tachycardia, dyspnea, agitation, confusion, and cyanosis progressing to unconsciousness. An allergic-like reaction ranging from rhinitis or angioneurotic edema to laryngeal or bronchial spasm or anaphylactoid shock may occur. Temporary renal shutdown or other nephropathy may occur.

Adverse reactions as a consequence of *excretion urography* include cardiac arrest, ventricular fibrillation, anaphylaxis with severe asthmatic reaction, and flushing due to generalized vasodilatation. Risks of *aortography* procedures include injury to aorta and neighboring organs, pleural puncture, renal damage (including infarction and acute tubular necrosis with oliguria and anuria), accidental selective filling of right renal artery during translumbar procedure in presence of preexistent renal disease, retroperitoneal hemorrhage from translumbar approach, spinal cord injury and pathology associated with syndrome of transverse myelitis, generalized petechiae, and death following hypotension, arrhythmia, and anaphylactoid reactions. In *pediatric angiocardiography*, arrhythmia and death have occurred. During *peripheral arteriography*, hemorrhage from puncture site, thrombosis of the vessel, and brachial plexus palsy (following axillary artery injection) have occurred. During *selective coronary arteriography* and *selective coronary arteriography with left ventriculography*, transient ECG changes (most patients); transient arrhythmias (infrequent); ventricular fibrillation (from manipulation of catheter or administration of medium); hypotension; chest pain; myocardial infarction; transient elevation of creatinine phosphokinase (occurred in about 30% of patients tested); fatalities have been reported; hemorrhage, thrombosis, pseudoaneurysms at puncture site, dislodgment of arteriosclerotic plaques, dissection of coronary vessels, and transient sinus arrest have occurred due to the procedure.

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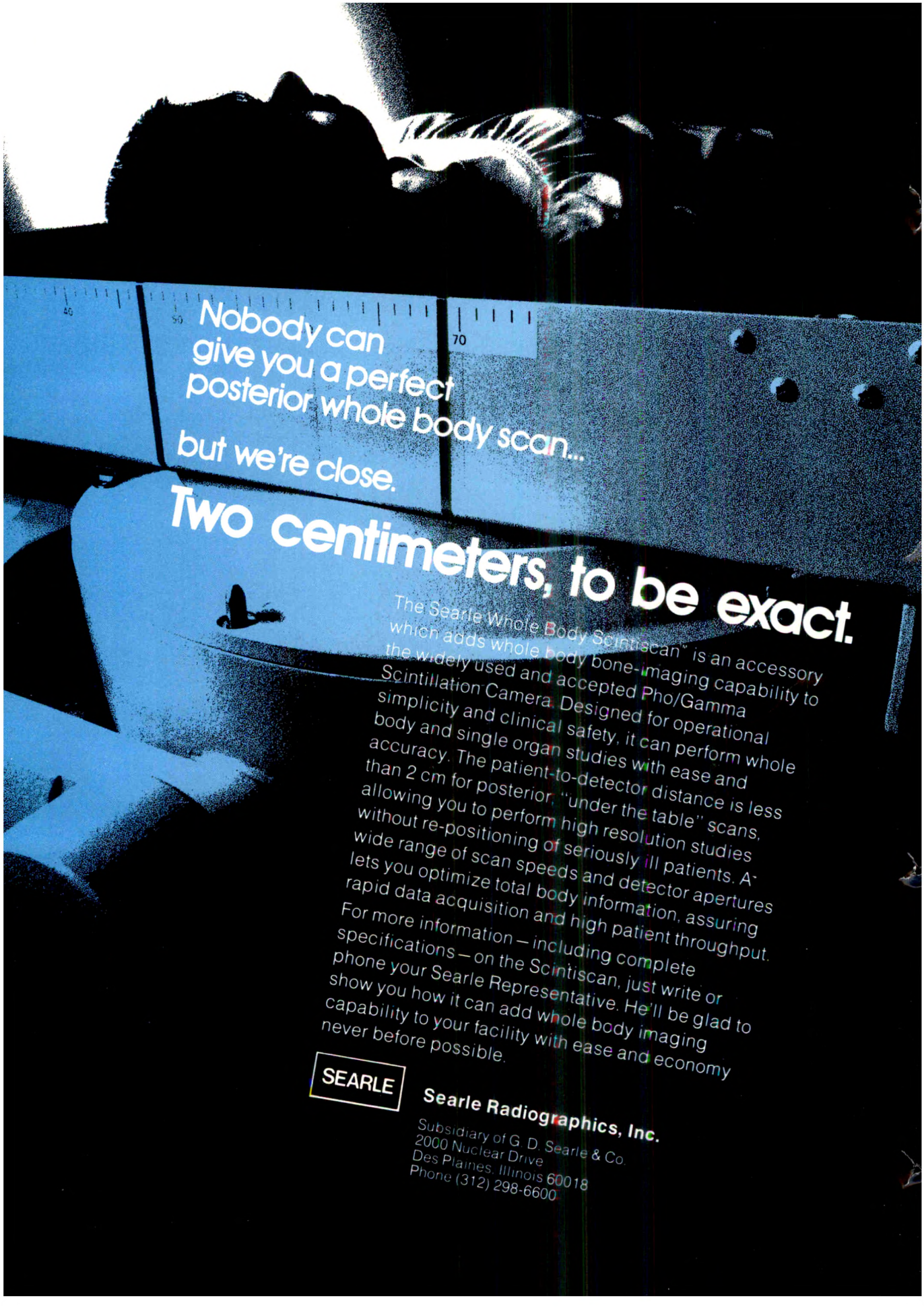

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RADIATION THERAPY OF MENINGIOMAS*

By WILLIAM M. WARA, M.D.,† GLENN E. SHELINE, M.D.,† HARRY NEWMAN, M.D.,† JEANETTE J. TOWNSEND, M.D.,‡ *and* EDWIN B. BOLDREY, M.D.§
SAN FRANCISCO, CALIFORNIA

MENINGIOMAS are among the more common tumors originating within the cranium. They account for 14.3 to 19 per cent of primary intracranial neoplasms.[14] Meningiomas are usually slow-growing, circumscribed lesions, which are often resectable. However, about 11 per cent of presumably completely extirpated tumors recur.[11] The question arises as to whether irradiation can reduce the recurrence rate of incompletely removed lesions.

Many investigators have stated that ionizing radiation is ineffective in the treatment of meningiomas.[4,6,13] McWhirter[10] reported that approximately 43 per cent of meningiomas were radiosensitive, especially those exhibiting extensive hyperostosis, a cerebral blood supply, and a multilobular form. More recently, King *et al.*[9] urged radiation treatment of incompletely removed meningiomas, especially angioblastic or sarcomatous types. Bouchard[2] advocates irradiation of meningeal tumors that are histologically malignant or clinically invasive. Because of such conflicting opinions we undertook an evaluation of the effect of radiation therapy in patients with meningiomas treated at the University of California, San Francisco (UCSF), from 1942 through 1972.

MATERIAL

The records of all patients in whom the diagnosis of meningioma was made from 1942 through 1972 were reviewed. Meningiomas constituted approximately 20 per cent of all intracranial neoplasms seen during the study period. In each case the pathological material was re-examined by one of us (J.J.T.) and the lesion classified according to the predominant cell type and pattern (Table 1), using the criteria of Rubenstein and Russell.[11,12] The majority of the lesions were transitional meningiomas (49 per cent) or syncytial meningiomas (33 per cent). We are in the process of reviewing and reclassifying these lesions according to criteria suggested by Boldrey.[1]

Most meningiomas occurred in the fifth or sixth decade of life. However, a wide

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From the Department of Radiology, Division of Radiation Oncology,† the Department of Pathology,‡ and the Department of Surgery,§ University of California School of Medicine, San Francisco, California.
Supported in part by National Institutes of Health Fellowship 1 FO1CA5293 8-01 from the National Institute of Cancer.

TABLE I

HISTOLOGICAL TYPE

Syncytial (meningotheliomatous)	72
Transitional (psammomatous)	106
Fibroblastic	18
Angioblastic	9
Meningeal sarcoma	5
Malignant meningioma	3
Total	213

range of ages was represented, the youngest patient being 6 years old and the oldest 82 years old at the time of diagnosis. Only 6 per cent of all patients with meningiomas were between 6 and 19 years of age. The majority of the lesions arose in the parasagittal-falx region, the cerebral convexity, or the sphenoid ridge; this incidence is comparable to that experienced by other investigators (Table II).

Of 213 patients (143 female and 70 male), who had meningioma, there were 10 in whom the tumor was discovered incidentally at autopsy and 15 who died during the immediate postoperative period. These 25 were excluded from our evaluation. The remaining 188 patients were treated by surgery with or without irradiation and are the basis of the following analysis.

TREATMENT

SURGERY

Total removal of the meningioma was effected whenever possible. When removal was thought to have been complete, no further therapy was given. If complete removal was not possible, there was removal of the maximum amount of tumor consistent with minimal damage from the operative procedure. In some instances incomplete removal was followed by irradiation. Whether radiation therapy was given depended upon the belief of the neurosurgeon regarding its effectiveness for a particular patient.

IRRADIATION

Until about 1950, orthovoltage equipment was usually used for radiation therapy, and the tumor dose was 3,000 to 4,000 rads. Since 1950, most patients have been treated with megavoltage irradiation using total doses of 4,500 to 5,500 rads, with daily increments of 180 rads given over a period of about $5\frac{1}{2}$ weeks.

RESULTS

Eighty-four patients (44 per cent) were treated by "total" surgical removal of the meningioma (Table III). None of them re-

TABLE II

DISTRIBUTION OF INTRACRANIAL MENINGIOMAS ACCORDING TO SITE

Site	Cushing and Eisenhardt[3]	Holub[8]	Earle and Richany[5]	Gautier-Smith[7]	Present Series
Parasagittal-falx	72	95	65	213	52
Convexity	54	74	61	315	42
Sphenoid ridge	53	49	56	124	59
Posterior fossa	23	18	18	57	25
Interventricular	6	7	4	14	4
Peritorcular	12	13	0	20	0
Intraorbital	1	1	0	9	0
Suprasellar	28	21	11	21	19
Temporal fossa	8	0	0	0	0
Olfactory groove	0	0	24	0	11
Diffuse	0	0	0	0	1
Other	0	0	4	0	0
Total	257	278	243	773	213

Table III

TOTAL SURGICAL RESECTION—WITHOUT IRRADIATION (84)

Interval Post Surgery (years)	Alive and Well	Died of Intercurrent Disease (no recurrence)
≤5	31	4
> 5–10	20	6
>10–20	7	3
>20	12	1
Total	70	14

Table IV

SUBTOTAL SURGICAL RESECTION—WITHOUT IRRADIATION (58)

Interval Post Surgery (years)	Alive and Well	Died of Intercurrent Disease (no recurrence)	Recurrence
≤5	9	0	27
> 5–10	2	1	9
>10–20	0	1	7
>20	1	1	0
Total	12	3	43

ceived postoperative irradiation. Fifty-eight per cent of these 84 patients have been observed for 6 years or longer and 27 per cent for at least 11 years. There has been no recurrence of a meningioma in this group of 84 patients.

Of the remaining 104 patients, 58 underwent subtotal removal of the tumor but did not receive postoperative irradiation (Table IV). The recurrence rate in these patients was 74 per cent. Sixteen patients with recurrence were subsequently irradiated (Table V): 7 are alive and well (1 to 9 years after radiation therapy), 6 died from the meningioma (1 to 11 years postirradiation), 2 died of intercurrent disease (8 and 18 years postirradiation), and 1 is alive with known persistence of the disease. The other 27 patients with recurrence were subjected to a second attempt at surgical removal of the lesion without irradiation: 5 are alive without further recurrence, 5 are alive with recurrence (1 to 19 years after reoperation), and 17 died from meningioma (1 to 18 years after reoperation).

Thirty-four patients underwent subtotal resection of tumor followed, as soon as the incision was healed, by irradiation (Table VI). There was a 29 per cent (10 of 34 patients) recurrence rate, with over half of the recurrences appearing within 5 years. Two patients were considered by us to have had inadequate irradiation; *i.e.*, a tumor dose of less than 5,000 rads. Of the 22 patients without recurrence, 14 have been observed 6 years or more and 10 for 11 to 30 years. Of the 10 patients who developed a recurrence, 2 are living after reoperation and the other 8 are dead because of the recurrence.

The remaining 12 patients underwent biopsy only or partial resection of tumor with postoperative irradiation and planned

Table V

TREATMENT OF RECURRENCES FOLLOWING SUBTOTAL RESECTION (43)

	Radiation Therapy	Surgery
Alive and well	7 (1–9 years*)	5 (1–23 years†)
Alive with the disease	1 (2 years)	5 (1–19 years)
Died (intercurrent disease)	2 (8 and 18 years)	0
Died of the disease	6 (1–11 years)	17 (1–18 years)
Total	16	27

* Period post therapy.
† Period postoperative.

Table VI

SUBTOTAL SURGICAL RESECTION WITH POSTOPERATIVE IRRADIATION (34)

Interval Post Surgery (years)	Alive and Well	Died of Intercurrent Disease (no recurrence)	Recurrence
≤5	8	2	6
> 5–10	4	0	1
>10–20	4	0	3
>20	6	0	0
Total	22	2	10

reoperation (Table VII). In each case, at the time of the initial operation, the tumor was considered not totally resectable, usually because of excessive vascularity. At the Cushing's Society Meeting in 1965 Boldrey advocated giving radiation therapy to decrease the vascularity of the tumor and assist in removal at reoperation. The tumor dose was 5,000 to 5,500 rads delivered in $5\frac{1}{2}$ to 6 weeks. Generally, an interval of about 6 months was allowed between irradiation and reoperation. Eight patients subsequently underwent total tumor resection; 7 are alive and well with no recurrence from 4 to 13 years after operation. In the other 4 patients, total resection of the meningioma remained impossible; 1 of these patients has subsequently died of the disease.

The treatment groups are classified in Table VIII according to histologic appearance of the tumor and treatment. The number of recurrences is shown in parentheses. No correlation is evident between histologic type and whether total resection was performed. Similarly, no correlation exists between histologic type and recurrence rate. It is possible that correlation may be found when the lesions are reclassified according to Boldrey's schema.

DISCUSSION

The natural course of a meningioma is long and variable. Furthermore, no available data exist for patients with comparable tumors who were randomized to receive or not receive postoperative irradiation. These factors make evaluation of the effect of postoperative radiation therapy difficult. Our data show that when a meningioma is thought at primary operation to be "totally resectable," the control rate by surgery alone approaches 100 per cent and irradiation is unnecessary, irrespective of the histologic type of the meningioma.

If, however, total extirpation of the tumor cannot be achieved because of its location, local invasion, adherence to vital structures, or excessive vascularity, it appears that benefit may be derived from radiation therapy. In our series, the over-all recurrence rate after subtotal removal of the tumor was 22 per cent for patients given postoperative irradiation to a tumor dose of at least 5,000 rads; this is in contrast to an over-all recurrence rate of 74

Table VII

BIOPSY OR SUBTOTAL RESECTION, IRRADIATION (PREOPERATIVE IRRADIATION), AND PLANNED REOPERATION (12)

Interval Post Surgery (years)	Total Removal at Reoperation		Subtotal Removal at Reoperation	
	Alive and Well	Died	Alive and Well	Died
≤5	1	0	1	1
>5–10	4	0	1	0
>10–20	2	1	0	1*
Total	7	1	2	2

* Died of intercurrent disease.

TABLE VIII

HISTOLOGY AND THERAPY*

Histologic Appearance	Total Resection	Subtotal Resection No Irradiation	Subtotal Resection with Irradiation	Preoperative Irradiation	Total
Syncytial	25 (0)	18 (14)	15 (4)	9 (1)	67 (19)
Transitional	43 (0)	28 (19)	15 (5)	3 (1)	89 (25)
Fibroblastic	9 (0)	8 (6)	—	—	17 (6)
Angioblastic	6 (0)	2 (2)	1 (0)	—	9 (2)
Meningeal sarcoma	0 (0)	1 (1)	2 (1)	—	3 (2)
Malignant meningioma	1 (0)	1 (1)	1 (0)	—	3 (1)
Total	84 (0)	58 (43)	34 (10)	12 (2)	188 (55)

* Numbers in parentheses represent subsequent recurrences.

per cent for those patients not irradiated. The difference in recurrence rates takes on added significance in that the post-treatment interval tended to be longer for those patients receiving irradiation as compared with those not irradiated; 53 per cent of those irradiated and 38 per cent of those not irradiated were observed longer than 5 years. Furthermore, as far as could be ascertained, these 2 groups of patients and their meningiomas were comparable. Since there were only 22 nonirradiated and 18 irradiated patients followed more than 5 years, 5 year recurrence free survival rates have not been calculated.

The salvage rate was higher (8 of 16) among those patients who at time of recurrence received irradiation (with or without reoperation). In as many as 17 (63 per cent) of the 27 patients reoperated but not irradiated, the meningiomas have already recurred. Radiation therapy is of value, therefore, in patients who have a recurrence following primary resection.

In the patients who have had biopsy and preoperative radiation therapy followed by a 6 month waiting period, the second, and definitive, surgical procedure appears to have been materially aided by the irradiation. Thus, 8 of 12 meningiomas initially deemed to be incompletely resectable because of the degree of vascularity became resectable, and 7 remain free of recurrence up to 13 years postirradiation.

CONCLUSION

On the basis of these data we conclude that: (1) if a meningioma can be totally resected, surgical excision is the treatment of choice; (2) if resection is incomplete, radiation therapy may prevent or markedly delay recurrence; (3) some previously nonirradiated recurrent meningiomas may be controlled by irradiation for extended periods of time; (4) the resectability of certain highly vascular meningiomas may be increased by preoperative irradiation; and (5) the value of radiation therapy appears unrelated to the histologic type.

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Vol. 123, No. 3

ENHANCEMENT OF THERAPEUTIC RATIO IN RADIOTHERAPY OF BRAIN NEOPLASMS*

By W. L. DeGINDER, M.D., *and* VITTHALBHAI MISTRY, Ph.D.
AUSTIN, TEXAS

IN primary and metastatic malignant brain tumors, survival more than 2 years after treatment is so uncommon that length of life is a poor measure of success. The early response and quality of life are relatively more important than in the case of malignancies in most other parts of the body. Surgical decompression, massive doses of corticosteroids, and powerful diuretics are often used to achieve prompt palliation.[4,19,22] Dangerously toxic drug combinations are now being added to radiotherapy in the hope of obtaining statistically significant improvement of survival.[28,32] Where these drastic measures are justifiable in the effort to increase therapeutic ratio just a few per cent, it is certainly justifiable to devote some effort and expense to modifications of radiotherapy methods that may enhance early response and reduce side effects without adding any potential hazard to the patient's comfort or his ultimate length of survival.

Since the advent of cobalt 60 and megavoltage x-ray generators, a variety of socio-economic and administrative pressures have encouraged radiotherapeutic practices that exploit the skin sparing character of these rays in order to reduce the number of fields treated daily on each machine. With such strong emphasis on the number of patient visits per day, it has grown more difficult to optimize dosimetry and fractionation for the individual patient. With the use of megavoltage radiation, acute reactions and delayed atrophic changes have moved below the surface, out of sight, and have ceased to be the indicators of "tolerance dose;" but radiation damage at and below the depth of maximum build-up takes on new importance. Excessive radiation damage in the first 2 or 3 cm. of normal tissue beneath the entry portal establishes the "tolerance dose" when brain tumors are treated with short-cut techniques.

CLINICAL MATERIAL

Clinical material will be described briefly for 2 purposes: (1) to qualify our opinions on this topic; and (2) to explain the absence of graphs and tables attempting to demonstrate superior survival in our experience with 129 patients given cobalt 60 teletherapy. From April 1965 through April 1973, 28 patients with a diagnosis of glioblastoma multiforme or Grade 4 astrocytoma were referred for postoperative radiotherapy. Nine neurosurgeons and several hospitals were involved in this referral pattern out of a 10 county region. It has not been possible to have all of the surgical material reviewed by one pathologist, but even allowing for irregularities of tumor grading, and assuming that some of these may have been Grade 3 neoplasms, we will show that it is significant that 7 of the patients survived 2 to 7 years from the time of treatment.

During the same interval, and from more diversified referral sources, we accepted 101 patients for radiotherapy of brain metastases. Although comparative survival studies are of doubtful value, it is significant that the median survival time from the end of treatment was 25 weeks and 8 patients lived more than 2 years.

For both types of intracranial malignancy, we recognize limited value in comparison of survivals, but our Grade 4 astrocytoma patients have faired no worse than those reported by Stage and Stein[30] (Fig. 1), and our patients with brain metastases have had median survivals corresponding to those reported by other authors re-

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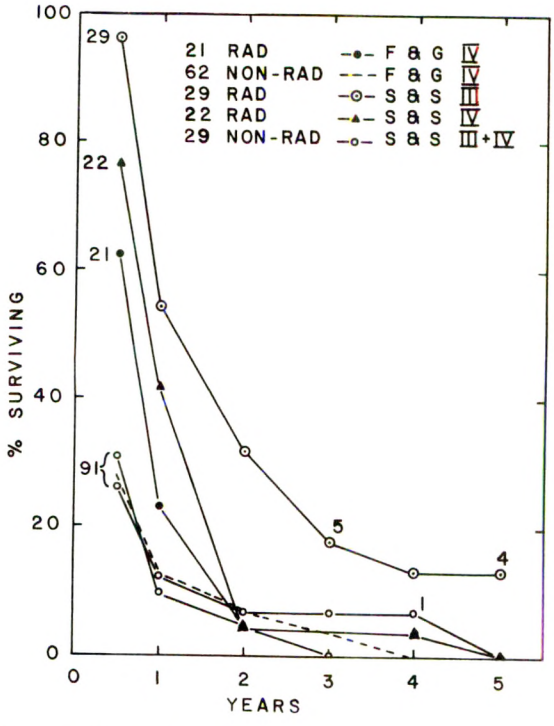

FIG. 1. Twenty-one patients with Grade 4 astrocytoma (glioblastoma multiforme) were treated between 1924 and 1952 (Frankel and German[14]). Stage and Stein[30] (1974) reported the fate of 22 treated since the availability of cobalt 60. Over the span of half a century, 91 nonirradiated patients had similar brief survivals. Two years after radiotherapy, comparison of survivals fails to indicate the actual superiority of newer methods.

cently.[12,24] For 16/28 astrocytomas and 59/101 metastases, referring physicians who have engaged in follow-up activity reported to our Cancer Registry palliative results from "good" to "excellent." Follow-up reports were obtained on all patients. These results have been obtained without the routine use of corticosteroids, without painful reactions of scalp and ears, and without permanent total or subtotal epilation which is often associated with chronic tenderness and atrophic changes of the scalp. Seventy-six per cent of the treatments were given on an outpatient basis (based on patient visits). A little over $\frac{1}{3}$ of the patients traveled more than 50 miles per treatment visit.

METHOD

The general plan of radiotherapy for brain tumors adopted in early 1965 deviated from the conventional and empirical practice of treating each patient 5 days per week:

1. For both groups, all but 9 patients received their entire treatment in 3 weekly fractions, with appointments on Monday, Wednesday and Friday, or on Tuesday, Thursday and Saturday.

2. From 3 to 5 converging fields were treated at each treatment session. Patients unable to cooperate well enough to permit the use of 3 or more converging fields in the first few days of treatment were started with coplanar opposed fields, both treated at each treatment session, then multifield plans were utilized as soon as clinical condition permitted.

3. For each patient, a plan was devised to give the maximum dose fraction per treatment at the estimated center of the primary malignant glioma or the dominant metastatic lesion according to all available localization data from neurologic evaluation, brain scans and arteriograms. Primary malignant astrocytomas and the intracranial metastases have been treated in similar fashion. Patients treated with intent to cure required a larger total dose and larger number of fractions, deliberately risking brain atrophy and gliosis in a zone surrounding the brain tumor. Prior to publication of NSD formula[10] tolerance was estimated on the basis of time-dose curves.[3,7]

4. Beam shaping blocks and eye shields were used routinely. We have observed further enhancement of therapeutic ratio (palliative response and scan evidence of tumor shrinking *vs.* radiation side effects and visible radiation damage) after discovering in May, 1973, the practicality of making Cerrobend alloy shaping blocks and compensating filters for routine use.[25]

RATIONALE

We believe that every patient deserves our diligent effort to obtain the best thera-

peutic ratio we can manage for his case. Tumor oxygenation rates, tumor response rates, and possibly some cure potentials are higher when the radiation dose in the tumor volume is more than the conventional 200 rads per fraction.[5,7,15,17,27] This seems most significant with large intracranial tumors producing distressing symptoms. Most patients with the malignant astrocytomas have surgical decompression prior to radiotherapy. Some of those with dominant metastatic tumors causing rapid progression of symptoms related to increasing intracranial pressure also require surgical decompression. Since corticosteroids temporarily reduce the mass, water content, and the sodium-potassium ratio of tumor in brain, about half of our patients have been started on corticosteroids prior to radiotherapy. Experience with 48 patients who had neither a craniotomy nor corticosteroids indicates that improved radiotherapy technique permits safe use of tumor dose fractions much larger than the conventional 200 rads per day: 118 of the 129 patients mentioned in this report received tumor dose fractions exceeding 300 rads per treatment day, and in the past 2 years we have used 400 to 500 rads per treatment day in selected cases. It appears that when a tumor receives 3 or 4 fractions of 500 rads each, or even 1,000 rads given in a single dose[16,19] the immediate shrinking of tumor counteracts any edema that may be produced by radiation, and patients with cerebral metastases usually show prompt symptomatic improvement without corticosteroids if necrosis and hemorrhage have not already reached disastrous proportions (Fig. 7).

The malignant astrocytomas are relatively uncommon, but at least 10 per cent of our cancer patients will at some time develop intracranial metastases. Gilbert Fletcher and co-workers at M. D. Anderson Tumor Institute have demonstrated that there is much to be learned through a careful analysis of treatment failures and complications.[12,28] These principles apply to brain tumors, and we believe they should be applied more strictly to palliative efforts than to intensive radiotherapy with intent to cure. Any avoidable distress or uncomfortable side effect from radiotherapy should be scored against the method. For the majority of patients with highly malignant primary or metastatic brain tumors, it is ultimately the improvement of functional capacity of the patient, the recovery of physical abilities, the recovery of his intellectual awareness and his conviction that he has been improved by treatment that should measure the success of a treatment plan. If the duration of survival can be prolonged for some of these patients without adding excess burdens or side effects, these might be scored as "extra points" in favor of the method. This type of evaluation lends further support to the philosophy that the manner in which each daily fraction is given is of more critical importance than a specified total dose. Where we are willing to use potent drugs such as BCNU and high doses of corticosteroids, or even these 2 together in combination with radiotherapy attempting to improve the therapeutic ratio, the daily technique of radiotherapy certainly deserves intense effort to put the maximum tissue effect just where it is needed.

In the early practice of radiotherapy, Baclesse, Coutard, and Regaud advocated the reduction of field size as treatment progressed, in order to permit the highest possible dose in the central portion of the tumor without causing excessive damage to surrounding normal tissue. Working with tumors that could be observed and palpated, they determined on the basis of clinical observation alone that the central portion of a tumor often required 20 to 25 per cent more radiation than the periphery of the tumor or its fine interstitial extensions, if local recurrence was to be prevented. The unique feature of brain tumors is that they are rigidly encased in the cranium. All brain tumors produce symptoms by 2 mechanisms: (a) the tumor infiltrates, displaces, and replaces brain substance; and (b), most tumors are sur-

rounded by an envelope of cerebral edema which produces additional neurologic disturbances. Because of its rigid confinement, the brain quickly exhausts its limited compensating mechanisms and then symptoms increase exponentially with the growing volume of tumor plus edema. On this basis alone there are advantages in *reversing* the sequence used by Baclesse, Coutard and Regaud. If one uses a schedule of *expanding* fields, with the first 20 to 25 per cent of a series of treatments concentrated into the symptom-producing tumor and its surrounding zone of cerebral edema, the vascular elements and other compensating mechanisms of the brain will remain relatively undisturbed, thereby enhancing the removal of edema and the flow of oxygen to the core of the tumor. If fields are then expanded to include the rest of the brain, the blood supply and normal portions of the brain are last and least affected by the radiation. The remainder of this paper will be devoted to discussion of other ways of accomplishing the same thing.

ISOEFFECT LINES

The concept of evaluating or predicting tissue radiation response by plotting iso*effect* lines instead of physical iso*dose* lines is not new. One of the authors first heard the idea discussed in 1948 by Charles L. Martin in connection with his method of treating cervical lymph node metastases.[8] He sought a better way to explain summation of effects from orthovoltage x-rays and the gamma rays from interstitial radium needle implants. At that time, almost everyone overlooked the significance of giving the x-ray treatments (2,100 r measured in air) in 6 fractions while the needles were still in place. A paper and exhibit at the 1970 International Cancer Congress first related two-dimensional plots of isoeffect lines to the Ellis NSD formula[6] to demonstrate limitations of physical isodose summations for the prediction or evaluation of late radiation damage in normal tissues.

In using the NSD concept, one has the freedom to specify how and where the full tolerance limit of normal tissues shall be determined. Delayed radiation sequelae that would be tolerable in one region of the body may be distressing or disabling in another. There are variations in the complication rates different radiotherapists find acceptable. Evaluation of anything more or less than tolerance requires calculation and comparison of partial tolerance values.[9,10,11,23] The tolerance level of normal tissues represents the limiting factor in radiotherapy of almost all malignant disease. No one has yet described a good way to predict or define specifications of "a tumor lethal dose" *in vivo*, but radiation effects in normal connective tissue and capillaries are quite consistent and easily measured.[10,11,21] The full tolerance dose for connective tissues and capillaries is related to the elapsed time (T) of a series of treatments, and to the number of fractions (N) into which the total dose (D) is divided according to the following formula:

$$D = (NSD)T^{0.11}N^{0.24}$$

At any point in normal tissue, the dose absorbed at each fraction is inversely related to N, and the dose at each fraction is about twice as important as the time factor in determining total cumulative radiation effect at that point.[6]

In a malignant cell population, radiotherapy given as a series of fractions results in relatively more damage than the same dose given as a single treatment because reoxygenation and apoptosis take place between fractions.[15,18] The number of clonogenic cells declines with each fraction and resistant anoxic cells become sensitive aerated cells for subsequent fractions. A number of authors[5,15,17,27,31] have shown that dose fractions larger than 200 rads (up to 600 rads) and intervals longer than 24 hours (up to 72 hours) improve the reoxygenation rate in a variety of experimental tumors. In any fractionation scheme, the number of viable clonogenic malignant cells per cc. within the irradiated column is reduced with each treatment. Up to a point,

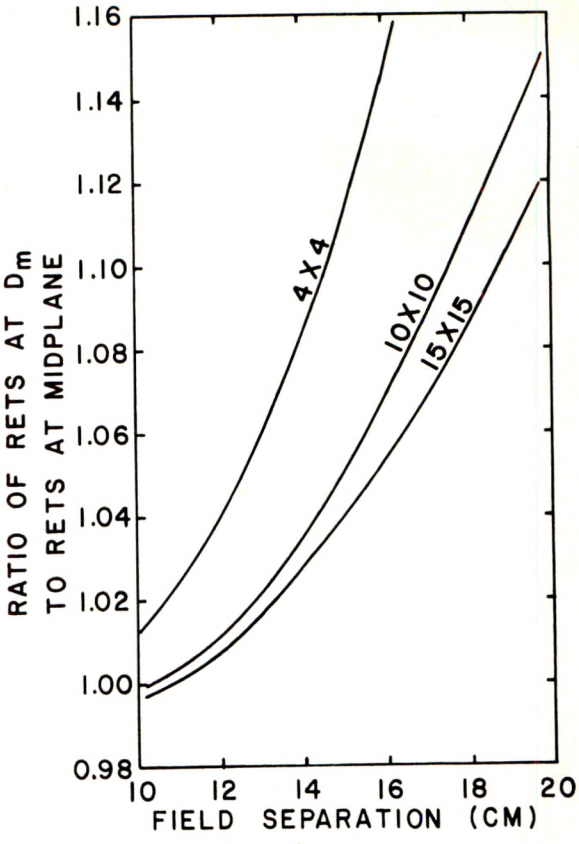

Fig. 5. 4 MV; 80 cm. SSD; coplanar opposed fields; both fields treated daily.

In the supervoltage energy range (cobalt 60 through 6 MV) changing field size from 100 sq. cm. to 225 sq. cm. has little effect on the ratios when treating opposed parietal fields with 13 to 16 cm. separation if both fields are treated each time.

⟹→

and deformity of normal brain structure. An envelope of edema which frequently surrounds these lesions tends to mask the true size and shape in this diagnostic method as in all others, but tomograms made 10 to 30 minutes after intravenous injection of sodium iothalamate (Conray®) reveals accumulation of the contrast material around the tumor, apparently at the junction of the actively growing portion of tumor and the surrounding edema. This same peripheral zone apparently accumulates the Tc^{99m} by which tumors are recognized in conventional isotope brain scans. Approximately 80 per cent of the intracranial malignancies can be demonstrated by isotope techniques. It should be noted

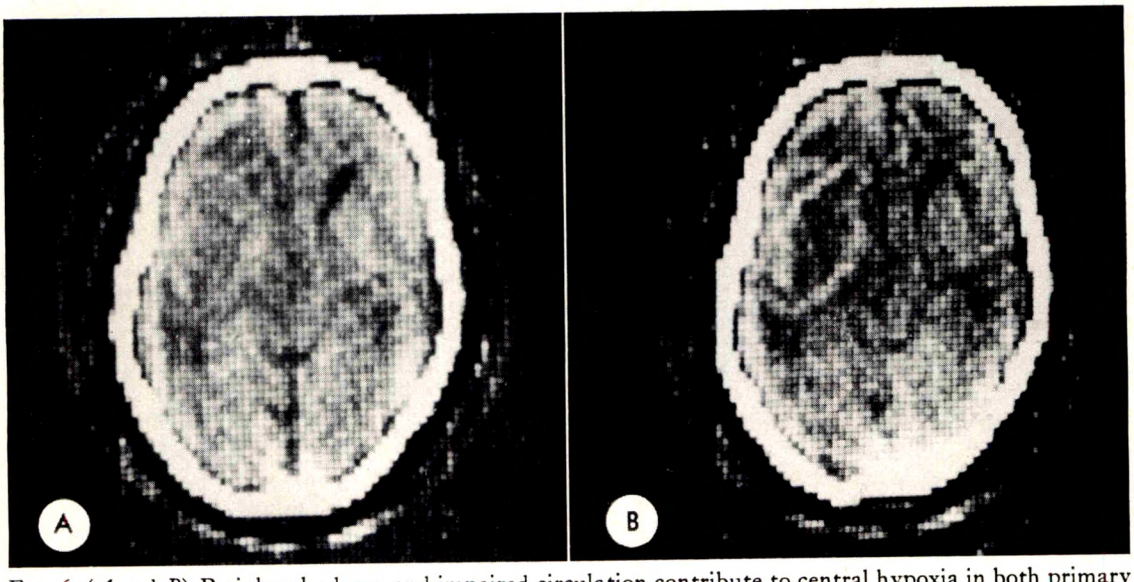

Fig. 6. (*A* and *B*) Peripheral edema and impaired circulation contribute to central hypoxia in both primary and metastatic tumors. Transverse axial tomograms made with the EMI scanner, reproduced by permission of James Ambrose,[1,2] show features that may appear with a dominant frontoparietal metastasis *or* a glioblastoma. Scan *A* shows tumor almost completely obliterating the frontal horn of the left lateral ventricle. Scan *B* of the same cross-section made 20 minutes after intravenous injection of 20 ml. of sodium iothalamate (Conray®) demonstrates what is thought to represent the junction of hypermetabolic periphery of tumor and the edema-zone. (Reproduced with permission of J. Ambrose and *Brit. J. Radiol.*[1])

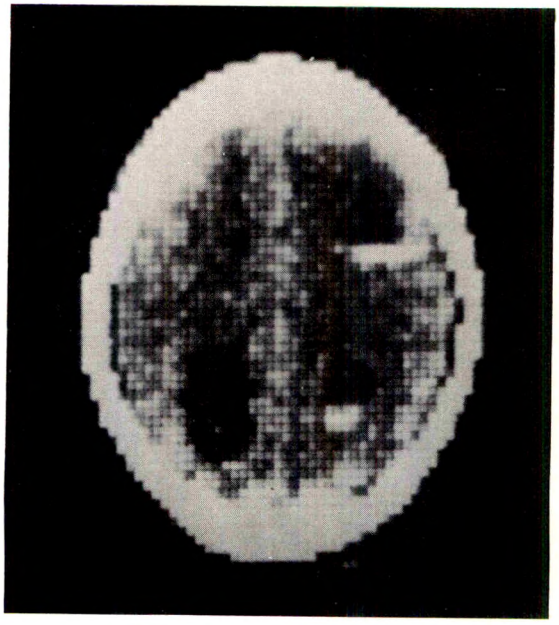

FIG. 7. Many metastatic tumors present with a dominant lesion having the same gross characteristics as a primary malignancy, with other intracranial metastases not detected until months later, or perhaps at autopsy. The EMI tomogram is made in "brow-up position," so liquid levels are sharply defined. These metastases from proven bronchogenic carcinoma show central cavities with liquefication and stratification of necrotic material in two of the three largest lesions. One may have eroded into the left lateral ventricle. Few patients are referred for palliative radiotherapy at this advanced stage.

that high doses of corticosteroids may interfere with isotope concentration, and satisfactory scans may be obtained a week or two after the medication is discontinued[13,22] or 2 or 3 days following start of radiotherapy.

In Figure 8 there are no features to indi-

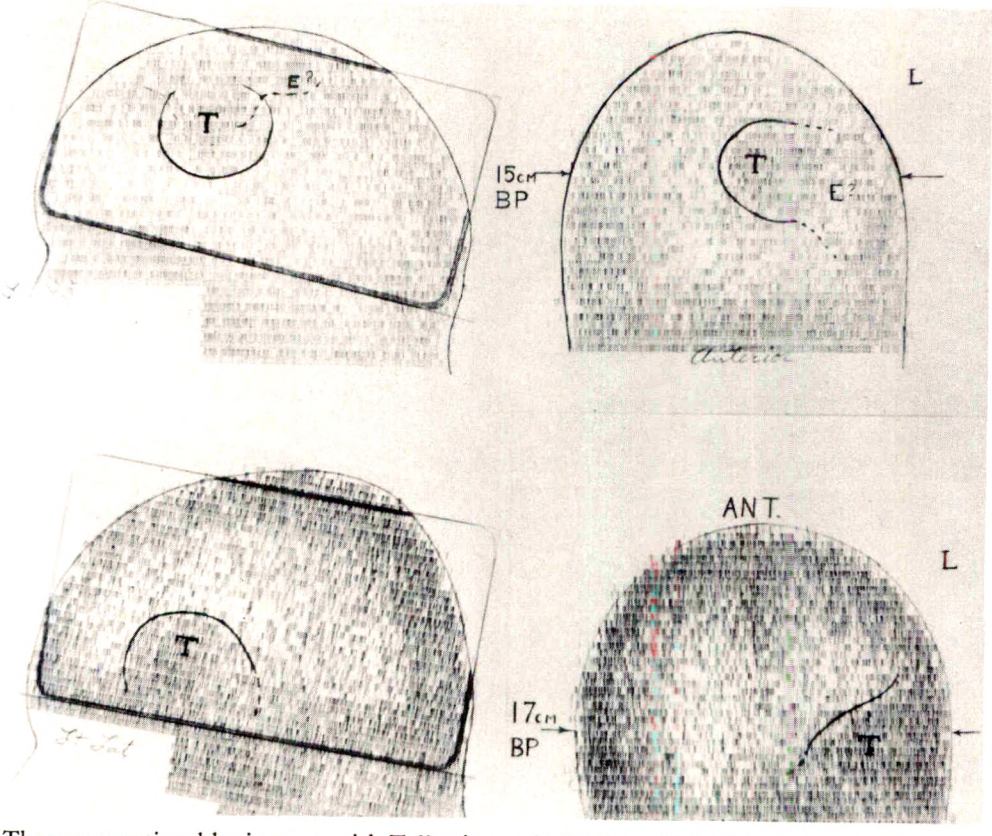

FIG. 8. These conventional brain scans with Tc^{99m} give no indication which of these patients has metastases from lung cancer and which has a malignant astrocytoma. Coplanar opposed fields suggested by the superimposed rectangular outlines are not the optimum plan of treatment for either one. Effort to optimize the distribution of the daily dose fraction is important in both cases.

cate which is metastatic carcinoma and which is proven Grade 4 astrocytoma. We believe that neither of these patients could get optimum results if treated with simple opposed fields suggested by the rectangular outlines. Knowing that symptoms tend to increase exponentially with increasing volume of the combined tumor and edema, giving the maximum radiation effect in the lateral cerebral cortex and the parietal vascular systems on both sides of the brain defeats the purpose of the treatment. Bouchard and others[4,20] have described some of the advantages of using 3 or 4 converging fields for treating brain tumors with supervoltage radiation. Visualizing radiation effects in terms of isoeffect lines illustrates advantages of optimizing radiation distribution so the tumor volume receives the largest dose fraction each time the patient is treated while the surrounding normal brain substance and vascular system get smaller fractions, thereby preserving or even enhancing the ability of the brain to cope with edema. The peripheral infiltrations of malignant astrocytomas, and the small asymptomatic implants of metastatic carcinoma are the least dangerous and at the same time most radiosensitive, so they should respond to a smaller dose fraction per treatment. Portions of brain considered to be uninvolved, or at least viable, need not receive more than the tolerance dose established on the basis of recovery of connective tissue and endothelium. Radiosensitivity of brain endothelium is probably of the same order of magnitude as endothelial and epithelial cells of other regions.[17,26] If radiation effect exceeds tolerance level in the tumor itself, or in the zone that has been subjected to severe edema for long intervals of time, there is probably no subsequent loss of *functioning* brain substance. Figure 9 illustrates how a simple arrangement of 4 unweighted rectangular fields improves the distribution of isoeffect lines in comparison with coplanar opposed fields. Our present knowledge of mathematics and radiation therapy allows much better optimization

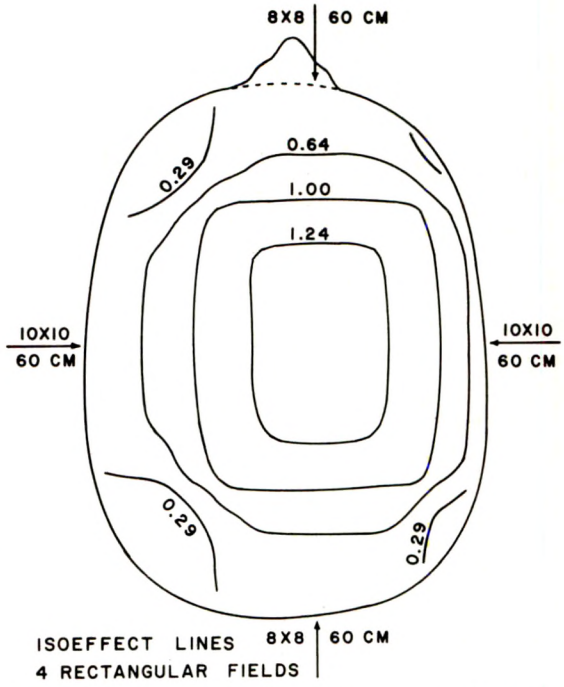

Fig. 9. As a first approximation, one may improve the distribution of isoeffect lines to favor reoxygenation and "sterilization" of the tumor with maximum repair and restoration of function in normal tissue simply by treating four fields for each tumor-dose fraction. Expanding field schedules, beam shaping blocks, missing tissue filters and isodose-optimizing techniques are refinements of total-brain or large-volume treatment plans.

of isoeffect distribution for large field or total brain radiotherapy.

Beam shaping blocks, and wedge filters to compensate for cranial curvatures, are refinements of multifield plans designed to treat large volumes or the total brain. The mechanics of attempting to optimize isoeffect distribution for total brain radiotherapy need not be prohibitively expensive or time consuming. The devices illustrated in Figure 10, *A* and *B* allow 4 cranial fields to be treated with the 4 MEV. linear accelerator in 15 minutes. Three Cerrobend® blocks provide beam shaping of all 4 fields and a wedge for missing tissue compensation is incorporated in the block that serves as beam shaper for both of the lateral fields. Isodose curves by film photodensitometry show attenuation at the top edge

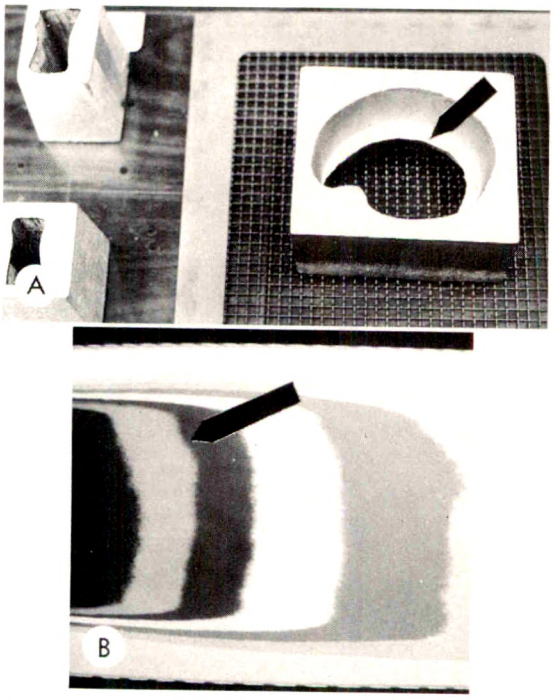

FIG. 10. Improvement of isoeffect distribution of the radiation at each total brain treatment session is not prohibitively expensive or time consuming. Three Cerrobend® blocks can provide beam-shaping and missing-tissue compensations of *four* beams. The arrow in the top right illustration indicates the thin compensating wedge cast into the block for both lateral fields, and its effect is seen along the top margin of the photodensitometer copy below. All 4 fields can be treated with the 4 MV linac in 15 minutes.

of the beam which eliminates the "hot spot" that would otherwise occur in normal tissues along the midplane from the brow to the occiput. After one side of the head is treated, the block and the patient are both turned over to treat the opposite side. Following treatment of the second lateral cranial field, the patient remains on his side and the beam shaping blocks for frontal and occipital fields go into the slot on the collimator face. Both are rigidly mounted on one piece of plastic. To complete the 4 fields, only the gantry needs to be moved, and the appropriate block lined up on the illuminated frontal and occipital fields.

CONCLUSION

For a given "tumor dose," the radiation effect and therapeutic ratio may be enhanced by the technique of daily fractionation. Full potential of teletherapy is achieved only when each fraction of the total treatment produces more radiobiological damage in the tumor than in normal tissues unavoidably irradiated. This requires 3 or more converging beams, all fields treated at each visit.

We believe that further refinements of optimization techniques are fairly obvious.[23] With very modest shop facilities, it is possible to construct a large variety of alloy blocks to shape and modify photon beams. The original design and construction of these devices requires several man hours, but there are at least 3 subsequent compensations: (1) the mechanism of set-up and treatment each day is greatly simplified so 3 or 4 fields can be treated in a very short time; (2) since accuracy is improved and some potential technical errors are eliminated, larger tumor doses can be given safely at each fraction; and (3) symptomatic and visible effects of radiotherapy are minimized or eliminated when the daily dose fraction in normal tissues has been deliberately minimized for each individual patient.

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We wish to acknowledge the assistance and encouragement from Dr. Frank Ellis, moral and financial support from the Austin Radiological Association. EMI scans are reproduced by permission of James Ambrose and the editors of the *British Journal of Radiology*.

APPENDIX

We shall define relative (biological) effect R.E.* as the ratio of the effective ret dose at a tissue site to the tissue tolerance ret

* R.E. should not be confused with relative biological effectiveness (RBE), which customarily is defined as the ratio of 250 kev. x-ray dose to test radiation dose required to produce equal biological effect.

dose. Ellis[9] calls it the biological effect ratio:

$$\text{R.E.} = \frac{\text{Biological dose at tissue site}}{\text{Tolerance dose of tissue}} = \frac{\text{ret dose}}{\text{NSD}}. \quad (1)$$

The line connecting points of equal R.E.s will be defined as the isoeffect line.[23] During a radiation treatment, the tumor and the surrounding tissue get different amounts of radiation dose per fraction. Thus a different number of fractions would be required to reach full tissue tolerance at different tissue sites, according to the Ellis NSD equation,[10] defined as:

$$\text{NSD} = \text{D} \cdot \text{N}^{-0.24} \cdot \text{T}^{-0.11}. \quad (2)$$

For convenience it can be reduced to

$$\text{NSD} = \text{d} \cdot \text{N}^{0.65} \cdot \text{k}^{-0.11}, \quad (3)$$

with $d = D/N$ and $k = T/N$. A tissue site that receives d′ rads per fraction would require N′ fractions to reach tolerance.† Using Equations (1) and (3) the relative (biological) effect R.E. at this tissue site when the desired number of fractions N prescribed for the tumor zone are completed is found to be:

$$\text{R.E.} = \frac{\text{N}}{\text{N}'}.$$

If 2 coplanar opposed fields are treated at each radiotherapy appointment, the combined isodose plot may be used to calculate a corresponding *isoeffect* plot for the dose per fraction absorbed at each isodose line during a series of treatments. However, when opposed fields are treated alternately (1 field per day) one must use the rad-per-fraction isodose plot of just one field, and for each isodose line calculate the partial isoeffect number.[9,23] When 2 such sets of curves opposing each other are summed, the resulting combined isoeffect plot shows the ratios of predicted cumulative effects in the normal endothelium and connective tissues relative to the cumulative effect at the midplane. The left half of Figure 2 shows the conventional physical isodose plot for the total treatment. The right half shows the isoeffect curves for opposed fields treated alternately to deliver a midplane dose of 5,000 rads in 5 weeks. The R.E. gradient from midplane to the maximum-dose region is much greater than the gradient in rads. The radiation effect in normal subcutaneous tissue will be 25 per cent greater than at the midplane where the tumor dose is often specified. The physical dose in the subcutaneous tissue is only 8 per cent above the midplane dose, but in terms of radiobiological effect, a relatively large volume of normal tissue would receive between 10 and 25 per cent higher effective dose than the "tumor dose."

With photon beams, the R.E. within the tumor and its immediate surrounding zone can be brought above the R.E. of the surrounding normal tissues only by means of multiple converging beams treated at each therapy appointment (Fig. 9), or through the use of moving beam techniques.

† Tolerance NSD designated as 1,800 rets at the 1.0 isoeffect line, equivalent to 6,100 rads, 30 fr./39 days—or 5,390 rads, 18 fr./39 days.

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EXTRANODAL NON-HODGKIN'S LYMPHOMAS OF THE HEAD AND NECK*

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EXTRANODAL presentations are common in patients with non-Hodgkin's lymphomas. Peters *et al.*[14] found the incidence to be as high as 61 per cent for reticulum cell sarcoma and 40 per cent for lymphosarcoma. Sixty-four per cent of 100 consecutive laparotomy staged patients in the series of Johnson *et al.*[9] were found to have extranodal disease. In the M. D. Anderson experience, primary extranodal presentations were seen in 58 per cent of Stage I and Stage II patients with diffuse non-Hodgkin's lymphomas treated between 1961 and 1969.[5] In 61 per cent of these cases, the extranodal sites were limited to the head and neck.

This report concerns a group of patients with extranodal presentations of non-Hodgkin's lymphomas in the head and neck who were admitted between 1947 and 1969.

MATERIAL

One hundred and twenty-eight previously untreated Stage I and Stage II patients, who presented with histologically proved non-Hodgkin's lymphomas in extranodal sites of the head and neck, have been reviewed (Table I). Sixty of these patients were treated prior to 1961 before lymphography was available for staging. Of the 68 patients admitted between 1961 and 1969, 34 were staged after lymphography. Although lymphography was used more routinely in the latter years, this procedure was seldom employed either in the very young or the very elderly. Laparotomy was not employed as a staging procedure in this series.

TABLE I

EXTRANODAL LYMPHOMAS OF THE HEAD AND NECK—STAGES I AND II

Patients admitted prior to 1961		60
Patients admitted from 1961 through 1969		68
Histology reviewed	58*	
Studied by lymphography	34	
		128†

* Constitutional symptoms, 2 patients.
† Stage I—55 patients; Stage II—73 patients. Males 79; females 49.

Fifty-five patients with disease clinically limited to extranodal sites were classed as Stage I. Seventy-three patients with associated disease in cervical lymph nodes were classed as Stage II.[2] The number of cases investigated by lymphography is shown in Tables VII and VIII for Stage I and II presentations. Constitutional symptoms, namely fever and night sweats, occurred in 2 patients: in 1 patient, the disease was clinically limited to the tonsil; the other had involvement of the nasopharynx and cervical lymph nodes.

Age and Sex. The peak age for male and female patients with extranodal lymphomas of the head and neck was in the seventh decade (Table II). Thirty-seven patients were between 60 and 70 years of age. Thirty-one patients were over age 70. Of 5 patients under age 20, 4 presented with disease in Waldeyer's ring. The youngest patient, age 3, was admitted with a lymphoma of the orbit. The oldest patient, age 95, was treated for a lymphoma of the tonsil. Of the total group of 128 patients, 79 were male and 49 were female, a

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TABLE II

DISTRIBUTION BY SITE AND AGE

Site	Age (years)				Total
	<20	20–39	40–59	≥60	
Waldeyer's Ring*	4	12	26	41	83
Paranasal Sinuses	0	0	2	10	12
Gum, Floor of Mouth, Gingivo-Buccal Sulcus, and Cheek	0	1	4	6	11
Thyroid	0	1	3	4	8
Orbit	1	1	1	2	5
Miscellaneous†	0	0	4	5	9
Total	5	15	40	68	128
[Rappaport Classification	2	4	13	39	58]

* Nasopharynx 27; tonsil 27; base of tongue 16; 2 or more component structures of Waldeyer's ring 13.
† Palate 4; parotid 3; pyriform sinus 1; larynx (subglottic) 1.

male to female ratio of approximately 3 to 2.

Presentation. The relative incidence by presenting site is shown in Table II. The most common site was Waldeyer's ring, which was involved in 83 of the 128 patients (65 per cent). Twenty-four of these patients (29 per cent) were classed as Stage I; 59 patients (71 per cent) were classed as Stage II. The incidence of cases with associated lymphadenopathy in the neck (71 per cent) was noted to be approximately the same as for squamous cell carcinoma.[12] Other primary sites were: paranasal sinuses, 12; gum and/or surrounding structures, 11; thyroid, 8; orbit, 5; hard palate, 4; parotid, 3; pyriform sinus, 1; and subglottic larynx, 1. Of this group of 45 patients, 31 (69 per cent) were classed as Stage I.

Presenting sites grouped under gum etc. were upper and lower gums, floor of mouth, gingivo-buccal sulcus, and cheek. Of 10 patients with presentations involving the lower gum and/or its surrounding structures, 3 had invasion of the mandibular branch of the fifth cranial nerve with local anesthesia, and 3 patients had direct invasion of the mandible.

Pathology. Slides on 127 patients in this study were submitted to the Department of Pathology for diagnosis. Prior to 1961, the importance of thin sections for study of lymphomatous tissue was not generally appreciated. Since the majority of the slides for this period were not satisfactory for sub-classification by either the cell type or the cellular pattern, the material for this time interval was not re-examined for 47 patients with an unequivocal diagnosis of lymphoma on admission. However, the slides were re-examined for 12 patients with a diagnosis of malignant neoplasm suspect lymphoma. Further study in 5 of these cases was rewarded with a definite diagnosis of diffuse histiocytic lymphoma. A sixth case was reclassified as malignant lymphoma type unspecified. In the other 6 cases, all of whom are deceased, the final diagnosis was lymphohistiocytic proliferation type uncertain.

For the period between 1961 and 1969, suitable material was available for reclassification according to the Rappaport system[15] in 58 of the 68 patients (Table III). Of the 58 cases reclassified according to the Rappaport system, 52 were diffuse lymphomas and 6 were nodular lymphomas (Table IV). Within the diffuse group, the distribution was histiocytic, 27; lymphocytic poorly differentiated, 12; mixed, 10; undifferentiated, 2; and lymphocytic well

Table III

HISTOPATHOLOGIC CLASSIFICATION—RAPPAPORT SYSTEM

Cell Type	Cellular Pattern	
	Diffuse	Nodular
Histiocytic	DH	NH
Mixed	DM	NM
Lymphocytic Poorly Differentiated	DLPD	NLPD
Lymphocytic Well Differentiated	DLWD	NLWD
Undifferentiated	DU	

differentiated, 1. In the nodular group, the material was classified as lymphocytic poorly differentiated 4, mixed 1, and histiocytic 1. The relation of specific histology to site and age is shown in Tables IV and V.

METHOD

TREATMENT

Technique. Prior to 1954, all patients were treated with kilovoltage irradiation. After 1954, the majority were treated with cobalt 60 teletherapy. Regardless of the energy of irradiation, the approach to treatment was dependent on the primary site, the status of the neck, and/or the likelihood of future disease in the neck. Patients with Waldeyer's ring presenta-

Table IV

DISTRIBUTION BY SITE AND HISTOPATHOLOGY IN 58 PATIENTS: RAPPAPORT SYSTEM*

	Total	Diffuse					Nodular		
		H	M	LPD	LWD	U	H	M	LPD
Waldeyer's Ring	37	18	3	8	1	2	1	1	3
Paranasal	5	3	1	1					
Gum, Floor of Mouth, Gingivo-Buccal Sulcus, and Cheek	3	2	1						
Thyroid	4	1	1	1					1
Orbit	2	1		1					
Miscellaneous	7	2	4	1					
Total	58	27	10	12	1	2	1	1	4

* See Table III.

Table V

RELATION OF HISTOPATHOLOGY TO AGE: RAPPAPORT SYSTEM*

Age (years)	Total	Diffuse					Nodular		
		H	M	LPD	LWD	U	H	M	LPD
<20	2			1		1			
20–39	4	2		1				1	
40–59	13	8	2	2			1		
≥60	39	17	7	9	1	1			4
Total	58	27	9	13	1	2	1	1	4

* See Table III.

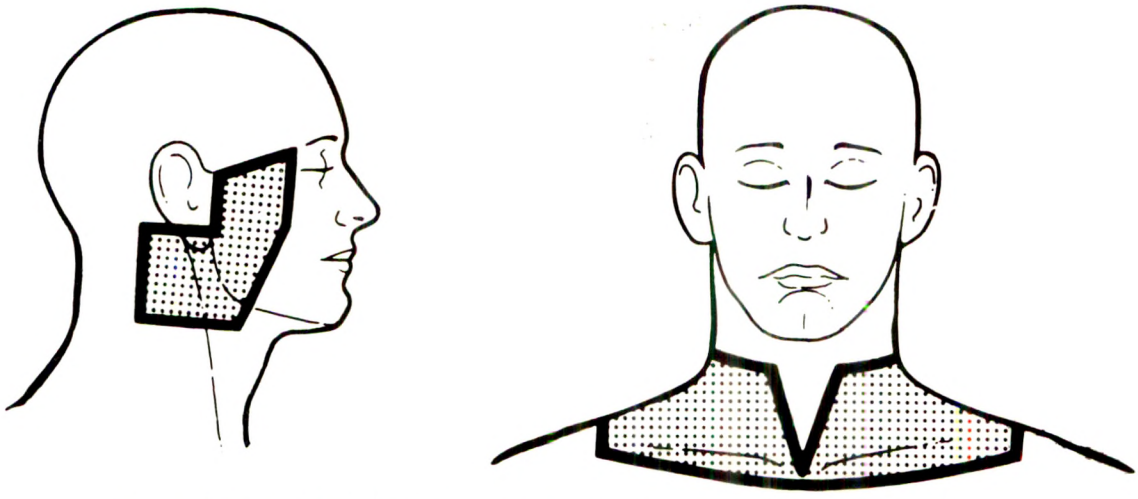

FIG. 1. Cobalt 60 fields for Waldeyer's ring, the neck and the supraclavicular fossae.

tions received treatment to the neck and the supraclavicular fossae in conjunction with the primary site regardless of the status of the neck (Fig. 1).[16] Because of the low incidence of subsequent cervical involvement in patients with other presentations, the neck was not treated prophylactically in these cases. Extensive involvement of the orbit and/or the paranasal sinuses was treated with wedge pairs (Fig. 2).[17] Thyroid presentations were treated with an anterior extended field to cover the neck and the mediastinum. A posterior field was used to augment the tumor dose calculated in the midplane of the mediastinum. Treatment fields for other presentations such as tumors of the gum, floor of the mouth, and pyriform sinus were individualized to suit the clinical situation.

Tumor Dose. The average tumor dose was approximately 4,000 rads. In general, this dose was delivered at a rate of 1,000 rads tumor dose per week. When indicated, additional treatment was given for residual disease. The maximum tumor dose for extranodal presentations, which included additional treatment for residual disease, was 6,500 rads. Only 3 patients received more than 6,500 rads for residual lymphadenopathy in the neck.

STATISTICAL ANALYSIS

Survival curves were calculated according to the method of Kaplan and Meier.[11] Gehan's modification of the generalized Wilcoxan test was employed to evaluate differences in survival curves.[6]

RESULTS

Local Control. Response to treatment in the primary site and the associated lymph nodes in the neck was analyzed for the 58

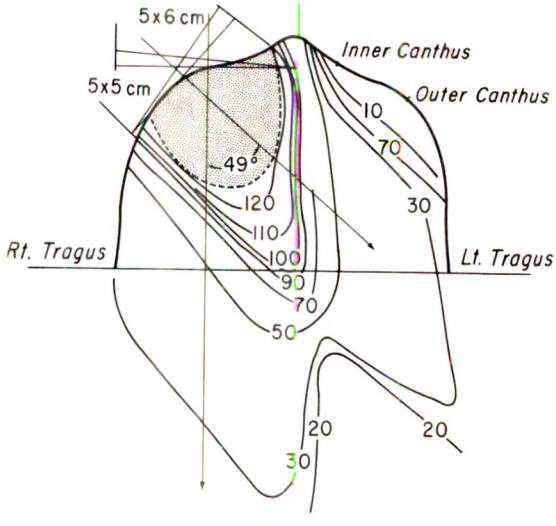

FIG. 2. Isodose distribution for an extensive lymphoma of the orbit. Cobalt 60, 80 cm. SSD, 60° wedge pair.

patients whose disease was reclassified according to the Rappaport system. For each dose level, the local control rate was approximately the same for both the histiocytic and non-histiocytic diffuse lymphomas. Despite additional treatment for residual disease, local control was not achieved in all patients who presented with massive involvement in either the extranodal site or the neck.[3] For the entire group, the over-all control rate was 83 per cent for extranodal sites as compared to 74 per cent for the neck. None of 6 patients with nodular lymphomas suffered from local recurrences (Table VI).

Survival. Survival curves were calculated to determine whether survival was influenced by age, presentation or stage of disease, histology, or lymphography. Of these, only age and stage of disease were shown to be significant (Fig. 4; and 5). No significant difference was found between the survival curves for patients staged clinically as compared to patients staged after lymphography ($p=.25$) (Fig. 3). The 5 year survival figures for these 2 groups were 53 per cent and 44 per cent, respectively. Survival for patients under age 40 was significantly better than for patients between the ages of 40 and 64 ($p=.01$) or for patients over age 64 ($p=.01$). The 5

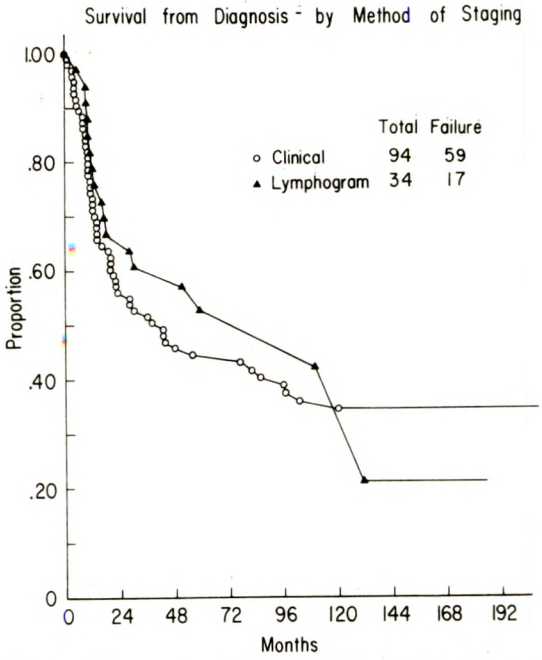

FIG. 3. The 5 year survival rates for the lymphogram studied group and the group not studied by lymphography were 53 and 44 per cent, respectively. The survival difference was not significant ($p=0.25$).

TABLE VI

LOCAL CONTROL BY HISTOLOGY AND MAXIMUM DOSE IN 58 CASES: RAPPAPORT SYSTEM

Maximum Dose (rads)*	Diffuse Histiocytic		Diffuse Non-Histiocytic		Nodular	
	Primary	Neck Nodes†	Primary	Neck Nodes†	Primary	Neck Nodes†
<3,000			1/1‡	1/1‡		
3,000–3,500		1/1	3/3	1/1	1/1	
4,000–4,500	2/3	2/3	6/7	5/7	3/3	2/2
5,000	11/12	4/4	7/9	2/2	2/2	1/1
5,500–6,000	9/12	2/4	3/4	2/3		
>6,000		3/4	1/1	0/1		1/1
Summary	22/27 (82%)	12/16 (75%)	21/25 (84%)	11/15 (73%)	6/6 (100%)	4/4 (100%)

* Summation of additional treatment to residual disease and dose delivered to the entire region. In general the total dose delivered to visible or palpable disease tended to be higher for patients who presented with extensive extranodal and/or nodal disease. Despite additional treatment, the incidence of local failure was somewhat higher than for patients with less extensive involvement who were generally treated to lower dose levels.

† Clinically positive and/or biopsy proven.

‡ Received a single dose of 1,000 rads.

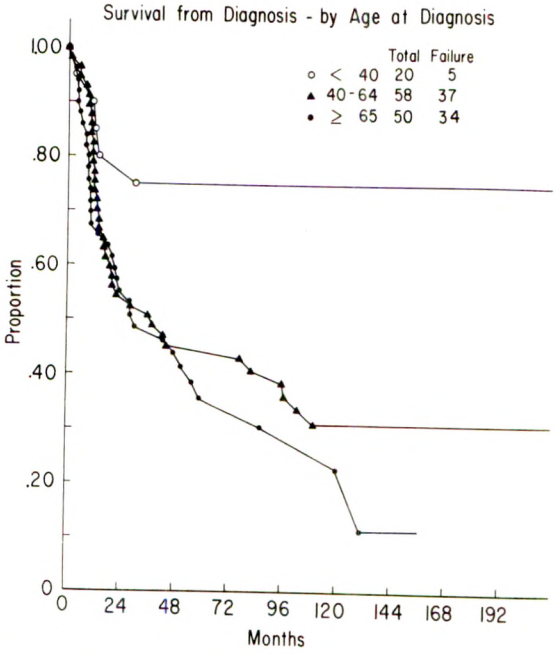

FIG. 4. Patients under age 40 at diagnosis experienced significantly longer survival than patients between the ages of 40 and 64 (p=0.01) and patients over age 64 (p=0.01). The corresponding 5 year survival rates were 75 per cent, 44 per cent, and 35 per cent, respectively. There was no significant difference in survival between the 2 older age groups (p=0.41).

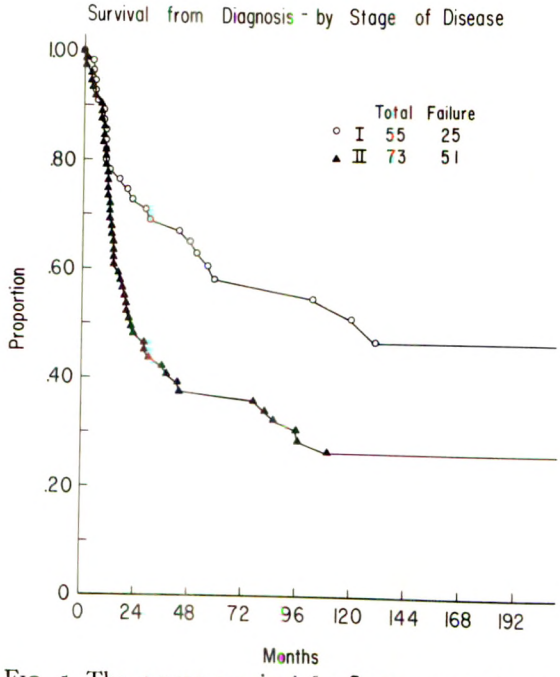

FIG. 5. The 5 year survival for Stage I was 58 per cent as compared to 37 per cent for Stage II. The corresponding 10 year survival figures were 51 per cent and 26 per cent, respectively. The survival difference was statistically significant (p=0.01).

year survival rates for the 3 age groups were 75 per cent, 44 per cent, and 35 per cent, respectively. No significant difference was demonstrated between the survival curves for the 2 older age groups (p=.41). The influence of stage at diagnosis is demonstrated in Figure 5. For Stage I, the 5 year survival rate was 58 per cent; for Stage II, the corresponding figure was 37 per cent. The difference between the survival curves for Stage I and Stage II patients was statistically significant (p=.01).

Virtually no difference was demonstrated between the survival curve for patients with involvement of Waldeyer's ring and the survival curve for patients with presentations in other sites (p=.93) (Fig. 6). The 5 year survival rates were 46 and 48 per cent, respectively. Although no statistical difference in survival was found between the total group of patients with

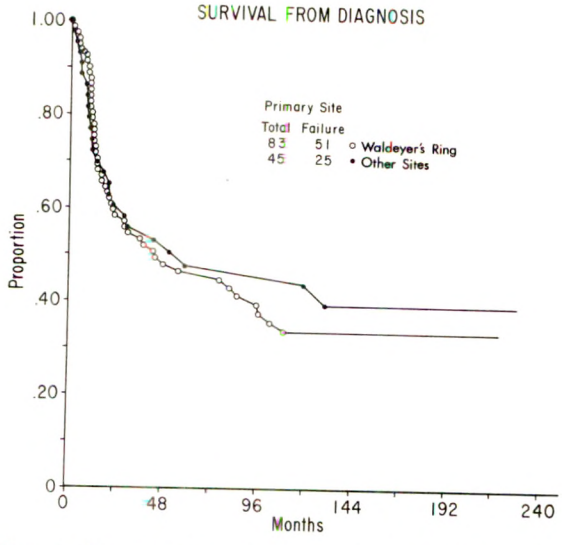

FIG. 6. The 5 year survival rate for the Waldeyer's ring group was 46 per cent as compared to 48 per cent for other sites. There was virtually no difference in the 2 survival curves (p=0.93).

involvement of Waldeyer's ring and the total group of patients with involvement of other sites, differences approaching significance were noted for presentations in the nasopharynx, faucial tonsil, and the base of the tongue. Five year results for patients with involvement of the base of the tongue were 66 per cent as compared to 38 per cent for the tonsil, 41 per cent for the nasopharynx, and 30 per cent for involvement of more than 1 of these sites ($p=0.13$, 0.18 and 0.09, respectively) (Fig. 7).

Although the 5 year survival rate for patients with diffuse histiocytic lymphomas was 30 per cent as compared with 49 per cent for patients with diffuse non-histiocytic lymphomas (Fig. 8), the difference in survival curves between the 2 groups was not significant ($p=.84$). Only 1 of 6 patients with nodular lymphoma is deceased.

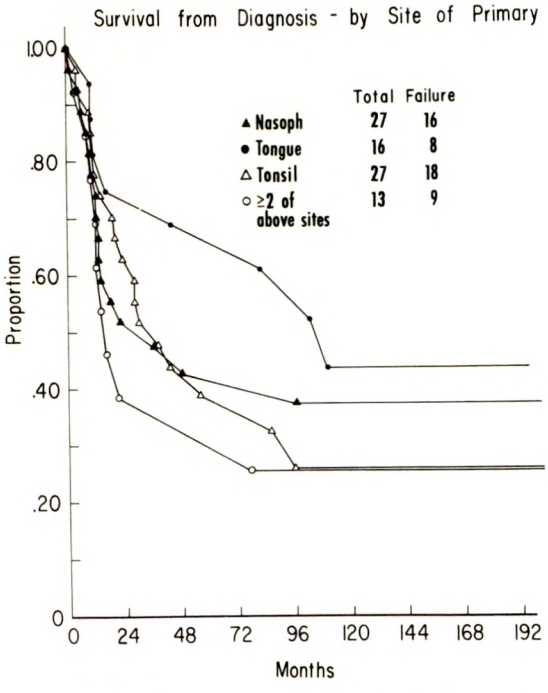

Fig. 7. Five year survival rates for base of tongue, nasopharynx, tonsil, and 2 or more component structures of Waldeyer's ring were 66 per cent, 41 per cent, 38 per cent, and 30 per cent, respectively. The difference in survivals approached statistical significance ($p=0.09$, 0.13, and 0.18 for base of tongue *versus*: 1. involvement of 2 or more of the component structures of Waldeyer's ring; 2. faucial tonsil; and 3. nasopharynx).

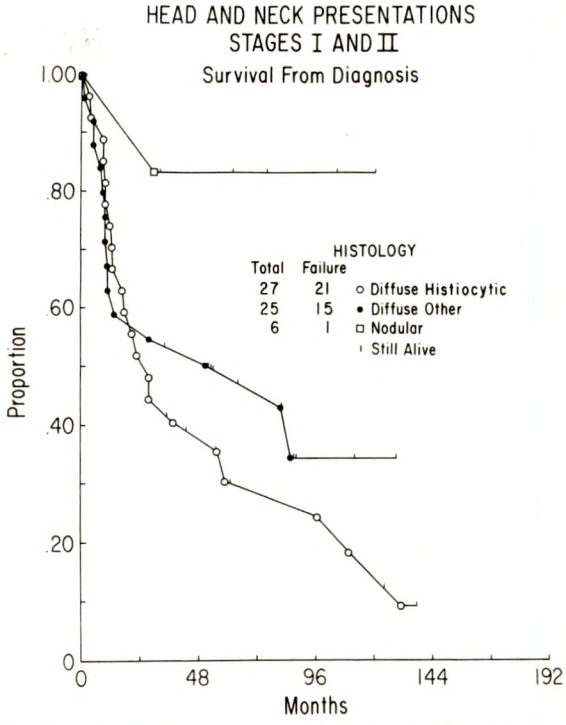

Fig. 8. Five year survival rates for diffuse histiocytic and nonhistiocytic lymphomas were 30 per cent and 49 per cent, respectively. The difference in survivals for these 2 groups was not statistically significant ($p=0.84$). One of 6 patients in the nodular group is deceased.

Patterns of First Major Manifestations of New Disease. The incidence of new manifestations of disease was related to the initial stage. In Stage I, 51 per cent (28 of 55 patients) had progression or local recurrence (Table VII). In Stage II, the incidence increased to 71 per cent (52 of 73 patients) (Table VIII). Of the total group of 80 patients with progression or local recurrence, information on initial new disease was available in 62 patients. Of these, disseminated disease was the most common initial manifestation (37 patients). Abdominal lymph nodes was the second most common site to be involved (14 patients). Secondary spread to the mediastinum was limited to 1 patient in Stage I, and 2 patients in Stage II.[10] Late local recurrence or persistent local disease as cause of death oc-

TABLE VII

PATTERNS OF FIRST MAJOR MANIFESTATION OF NEW DISEASE STAGE I—EXTRANODAL SITES

Site	No. of Cases	No Subsequent Disease	Local Recurrence	Med.*	Med. and Abd.*	Abdomen†			Disseminated	Unknown
						LN	GI	Liver		
Waldeyer's Ring	24 (6)	14 (6)	1				1		5	3
Paranasal Sinuses	9 (3)	4 (1)				1		1	3	
Gum, Floor of Mouth, Gingivo-Buccal Sulcus, and/or Cheek	8 (2)	3 (0)		1		1			1	2
Thyroid	4 (0)	3 (0)	1							
Orbit	3 (0)	1 (0)							2	
Miscellaneous	7 (2)	2 (1)	1			1			1	2
Total	55 (13)	27 (8)	3	1		3	1	1	12	7

* Med.—Mediastinum; Abd.—Abdomen.
† Abdominal involvement: LN—Limited to lymph nodes; GI—GI tract alone or with nodal disease; Liver—Liver with or without lymph node and/or GI involvement.
( ) Number of patients studied by lymphangiography.

curred in 2 patients. Recurrence in the primary site prior to evidence of progression was seen in 3 patients (Tables VII and VIII).

Approximate Time from Admission to Progression of Disease. The time interval to progression of disease was documented in 62 patients as follows: less than 1 year, 34 patients (55 per cent); 1 to 2 years, 19 patients (31 per cent); 3 to 4 years, 5 patients (8 per cent); and 5 years or more, 4 patients (6 per cent) (Table IX).

Management of Long-Term Survivors with Progression. The time interval to development of new disease was compared to subsequent survival in 13 long-term survivors with progression (Table X). Of these 13 patients, 5 are alive 2 or more years after discovery of new disease. Two of these patients are of particular interest. One 3 year

TABLE VIII

PATTERNS OF FIRST MAJOR MANIFESTATION OF NEW DISEASE STAGE II—EXTRANODAL SITES PLUS NECK NODE(S)

Site	No. of Cases	No Subsequent Disease	Local Recurrence	Med.*	Med. and Abd.*	Abdomen†			Disseminated	Unknown
						LN	GI	Liver		
Waldeyer's Ring	59 (17)	16 (6)		2	2	8	3		22	6
Paranasal Sinuses	3 (1)					3				
Gum, Floor of Mouth, Gingivo-Buccal Sulcus, and/or Cheek	3 (0)		2						1	
Thyroid	4 (2)	2 (1)							2‡	
Orbit	2 (1)	1 (0)						1		
Miscellaneous	2 (0)	2 (0)								
Total	73 (21)	21 (7)	2	2	2	11	3	1	25	6

*†( ) See Table VII.
‡ Both developed pulmonary metastases, one with spread to the pancreas.

TABLE IX

APPROXIMATE TIME FROM ADMISSION TO PROGRESSION OF DISEASE*

Extranodal Site	Years						Total
	<1	1	2	3	4	≥5	
Waldeyer's Ring	22	11	4	1		3	41
Paranasal Sinuses	4	3			1		8
Gum, Floor of Mouth, Gingivo-Buccal Sulcus, and/or Cheek	3		1		2		6
Thyroid	3						3
Orbit	2					1	3
Miscellaneous				1			1
Total	34	14	5	2	3	4	62

* Not included—1 patient dead of late local recurrence only.
1 patient dead of persistent local disease.
3 patients with local recurrence prior to progression.
13 deceased patients with no follow-up as follows: dead under 1 year, 7 patients; dead at 1 year, 2 patients; dead at 2 and 3 years, 2 patients; dead at 5 years or more, 2 patients.
48 patients with no evidence of progression.

TABLE X

MANAGEMENT OF LONG TERM SURVIVORS WITH PROGRESSION

Primary Disease	Initial New Disease			Treatment of New Disease*					Current Status Post Treatment for New Disease*
		Site(s)*	Years After Admission	None	XRT	Chem	XRT-Chem	Surg	
Waldeyer's Ring		Brain, epidural space	1		X				NED 14 years
	7	Dorsal vertebrae	3		X				NED 2 years
		Diffuse	4	X					Dead <1 year
		Abd. and local recurrence	7	X					Dead <1 year
		Stomach	7			X			Dead <1 year
		Stomach	8					X	Postoperative death
		Diffuse	9	X					Dead <1 year
Sinuses	1	Vertebral column	4	X					Dead at 7 years
Gum, etc.	2	Abdomen	4	X					Dead <1 year
		Mediastinum	5				X		LWD at 9 years
Orbit	2	CNS leukemia	1				X		NED 3 years
		Med. and abdomen	9	X					Dead <1 year
Misc.	1	Abdomen	3		X				LWD at 11 years
Total	13	patients	1–9 years	6	3	1	2	1	1–14 years

* XRT—radiotherapy; Chem—chemotherapy; Surg—surgery; NED—no evidence of disease; LWD—living with disease; Abd.—abdomen; Med.—mediastinum; CNS—central nervous system.

TABLE XI

COMPLICATIONS IN 8 OF 128 PATIENTS

Complication	Primary Site Treated	Result
Central Nervous System		
Brain stem necrosis	Waldeyer's ring	Dead <10 months
Transverse myelitis	Larynx	Dead at 8 months
Paresis of lower extremity	Thyroid	NED-11 years
Eye		
Endophthalmitis	Waldyer's ring and orbit	Enucleation
Endophthalmitis*	Antrum	Enucleation
Endophthalmitis	Antrum	Enucleation
Maxilla—necrosis	Nasal cavity and ethmoid sinus	Conservative treatment. NED >4 years
Mandible—necrosis	Gum with tumor invasion of mandibular nerve	Conservative treatment. NED 15 years

* Evisceration of orbital contents

old child treated for a poorly differentiated diffuse lymphocytic lymphoma of the orbit developed leukemia of the central nervous system at 1 year. Treatment with a combination of chemotherapy for leukemia and radiotherapy to the central nervous system resulted in a complete remission which has been continuous for 36 months. The other patient was treated at age 15 for a lymphoma of the tonsil. One year later this patient developed evidence of new disease in the mid-brain which was treated definitively with total brain irradiation. Six months later the same patient developed paraplegia secondary to an epidural mass in the mid dorsal region of the spinal canal. Again, treatment was definitive radiotherapy. Since then, this man has been clinically free of disease for 14 years, and he has no residual disability.

One deceased patient of interest was an 83 year old female who received treatment for a diffuse histiocytic lymphoma of the antrum. Four years later, this patient developed radiographic evidence of vertebral involvement. Although she received no further treatment, she survived another 7 years. Death followed a pathologic fracture of the hip.

Complications. Major complications were directly attributable to radiation therapy in 6 patients. In 2 patients, complications were due to factors related to the disease in addition to irradiation. The clinical features of these 8 cases are shown in Table XI.

DISCUSSION AND CONCLUSIONS

A histologic review of 58 cases of Stage I and II extranodal lymphomas of the head and neck revealed a 90 per cent incidence of diffuse lymphomas. Approximately 50 per cent of these cases were histiocytic. Regardless of the histologic sub-type, or whether lymphography was used for staging, survival for patients treated with radiotherapy to clinically involved regions was generally unsatisfactory. For patients over age 40, the 5 year survival figure was only 53 per cent for lymphogram studied cases.[1,4,5] Approximately one-third of all patients developed new disease within the first year. Regardless of the time interval, subsequent progression was not recognized until the disease had disseminated widely in the majority of patients. This latter finding is in keeping with our previous observation that diffuse dissemination is the commonest manifestation of new disease in Stage I and II patients with diffuse lymphomas presenting in lymph nodes.[5]

The fact that early dissemination has been shown to be the most common initial

manifestation of new disease for both nodal and extranodal presentations of Stage I and Stage II diffuse lymphomas, is evidence of a need for a new approach to treatment. Because a significant number of lymphogram negative patients may have involvement of mesenteric lymph nodes and/or the gastrointestinal tract, staging celiotomy should be routine for patients with either nodal or extranodal presentations of Stage I or Stage II disease under age 65, unless medically contraindicated. For celiotomy Stage I and Stage II patients, our opinion is that these patients should be involved in clinical trials to determine whether results of intensive radiotherapy to involved regions can be improved by the addition of a combination of multiple chemotherapeutic agents.[8,13]

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IMMUNOSUPPRESSION FOLLOWING RADIATION THERAPY FOR CARCINOMA OF THE NASOPHARYNX*

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SUPPRESSION of cell mediated immunity following irradiation has been reported by several investigators.[2,3,8,9,11,13] Stjernsward *et al.*[12] reported depressed cell mediated immunity as measured by T-cell rosette formation and lymphocyte stimulation with phytohemagglutinin (PHA) in patients receiving postoperative parasternal irradiation for breast carcinoma. Levy and Kaplan[7] recently noted impaired lymphocyte response to PHA in previously irradiated patients with Hodgkin's disease. The majority of the reported cases had large fields and/or mediastinal (thymic) irradiation.

We have evaluated patients with nasopharyngeal carcinoma prior to initiation of therapy. All 11 patients presented with elevated serum immunoglobulin A and 6 of 11 with depressed cell mediated immunity. The relationship between head and neck irradiation and further suppression of cellular immunity in patients with nasopharyngeal carcinoma was investigated.

MATERIAL AND METHOD

PATIENTS AND TREATMENT

Eleven consecutive patients with nasopharyngeal carcinoma were prospectively evaluated at the University of California San Francisco. All patients received standard radiation therapy treatment using a 4 mev. linear accelerator with a tumor dose to the nasopharynx of 6,500–7,000 rads and a tumor dose to the cervical-supraclavicular lymph nodes of 6,000 rads. The daily fraction was 180 rads tumor dose and the total treatment time approximately 8 weeks.

IMMUNOLOGIC EVALUATION

An immunologic profile was generated pre- and post-treatment for each patient. All tests were performed prior to the initiation of radiation therapy, and repeated 1 month following completion of therapy. Serum immunoglobulins were quantitated by single radial diffusion using a modification of the Mancini technique, with World Health Organization reference serums for standardization. Patients were immunized with 50 μg. of polyvalent pneumococcal polysaccharide vaccine* (PPS) and 100 μg. of keyhole limpet hemocyanin† (KLH), and 2 weeks later a serum specimen was obtained for hemagglutination titer. Total lymphocyte counts were obtained. Peripheral lymphocytes were isolated using a hypaque-ficoll gradient. After isolation of lymphocytes, *in vitro* stimulation with phytohemagglutinin (PHA) and formation of T-cell rosettes were performed using our previously described techniques.[1] Patients also had skin tests placed to evaluate delayed hypersensitivity including intermediate strength PPD, mumps, candida, and streptokinase-streptodornase (SKSD).

RADIATION DOSIMETRY

The distribution of dose in the thymus region was determined using a tissue-equivalent man phantom,‡ and thermoluminescent dosimeters. The phantom was sectioned in 2.5 cm. slices with holes drilled

* Eli Lilly and Company.
† Pacific Biomarine Supply Company.
‡ Rando Average Man.

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Table I

IRRADIATION CONDITIONS

Site	Field Description	Comments	Field Size (cm.)	Mid-Plane Dose (rads)
Nasopharynx	Left Lateral 1		17×20	2,500
	Right Lateral 1		17×20	2,500
	Left Lateral 2		10.5×7	900
	Right Lateral 2		10.5×7	900
Cervical-Supraclavicular	Anterior 1	Mid-Plane Bar Used	6×20	5,000
	Anterior	Same Inferior Border as 1	12×20	540
	Posterior		12×20	540

for the dosimeters in a 3×3 cm. grid. The dosimeters were Throwaway LiF capsules which have good linearity of response up to at least 1,000 rads, and are capable of moderate precision.[5] The fields used and the given doses are shown in Table 1. In making the measurements, typical field sizes appropriate to the dimensions of the man phantom were used. All fields used for normal treatment were irradiated even though some were far from the region of measurement, since we wanted to include the contribution of scattered, as well as direct, irradiation.

RESULTS

The measured doses in terms of mean and standard deviation of the measurements both outside and beneath the midline bar are given in Table II. They are presented as measured longitudinally from the suprasternal notch (SSN). The edge of the supraclavicular fields was approximately 3.4 cm. from the SSN in the midline. Grant[4] gives the usual location of the adult thymus as approximately 2 cm. superior to the SSN and 4–5 cm. inferior to the SSN.

All patients evaluated had elevations of serum IgA prior to therapy. The range was 300 mg./100 ml. to 1,000 mg./100 ml. with a mean of 533 mg./100 ml. There was no apparent change in this value after irradiation. Antibody mediated immunity was judged to be intact in that all the patients responded to immunization with PPS or KLH, or both, with a greater than 2 fold increase in titer.

Following irradiation all patients had suppressed cell mediated immunity (Table III). All patients had depressed total lymphocyte counts. The average pre-treatment number was 1,714, and the average post-treatment number was 683, a reduction of 60 per cent. Following therapy, 8 of 11 patients had depressed T-cell rosettes, and 9

Table II

DOSE MEASUREMENTS AT MID-PLANE

Longitudinal Distance Inferiorly from Suprasternal Notch (cm.)	−2.5	0	2.5	5.0	7.5	10.0	12.5
*Measured Mean Dose and Standard Deviation (rads)	5,150±950 (3,000)	4,480±540 (890±63)	4,040±380 (690±34)	390±40	170±30	120±7	90±7

* Dose measured beneath mid line bar is given in parentheses.

TABLE III

CELL MEDIATED IMMUNITY

Patient Stage* Normal Values:	Pre-Therapy				Post-Therapy			
	Total Lymphocyte Count (1,500 ± 200)	PHA (27,290/538 ± 10,005/73)	Index†	T-Cell Rosette (55% ± 5%)	Total Lympho-cyte Count	PHA	Index	T-Cell Rosette
1. $T_1N_0M_0$	1,007	16,404/355	46	58%	705	6,214/77	81	15%
2. $T_1N_0M_0$	1,622	25,973/444	59	36%	1,020	1,441/121	12	44%
3. $T_1N_0M_0$	2,323	1,369/35	39	—	588	2,800/127	22	41%
4. $T_1N_1M_0$	2,272	13,576/160	85	67%	987	4,869/14	348	55%
5. $T_1N_1M_0$	2,028	45,277/439	103	66%	594	3,644/63	58	64%
6. $T_1N_2M_0$	1,952	2,338/18	130	—	850	1,900/120	16	25%
7. $T_1N_2M_0$	2,640	26,750/595	45	48%	336	—		73%
8. $T_2N_0M_0$	1,224	5,911/119	50	45%	330	4,060/209	19	58%
8. $T_2N_2M_0$	1,224	79/35	2	—	481	4,725/410	12	38%
10. $T_2N_3M_0$	1,606	13,200/349	38	60%	868	4,334/293	15	46%
11. $T_4N_0M_0$	960	5,130/112	46	24%	750	22,962/642	36	46%

* Patients staged using classification of Moench and Phillips.[10]
† Index = stimulated counts/resting counts.

of 10 had abnormal lymphocyte response to PHA.

DISCUSSION

Since the early reports of lymphopenia following postoperative treatment for breast carcinoma, many possible mechanisms have been proposed to explain the effects of irradiation on the immune system. The majority of the explanations have implicated irradiation of the thymus gland and subsequent deficiency in cellular immunity. However, O'Toole *et al.*[11] and Chee *et al.*[3] reported lymphopenia and decreased lymphocyte stimulation with PHA in patients following irradiation to fields not containing the thymus gland. Both groups of investigators suggested that the observed suppression of cellular immunity was related to irradiation of large blood volumes in the treatment field.

O'Toole *et al.*[11] evaluated patients prior to and following irradiation of the bladder. Chee *et al.*[3] studied individual cases of esophageal, breast, testes, lung, ovary, and bone cancer and found suppressed cellular immunity as measured by lymphocyte stimulation by PHA in all patients except 1 who had received local irradiation to a femur. In addition to measuring patient lymphocyte response to PHA *in vitro*, they incubated normal donors' lymphocytes with patients' serum and demonstrated normal lymphocyte response to PHA; thus, they excluded the possibility that irradiation produced a toxic serum factor which was responsible for suppressed cellular immunity.

Of interest in relation to our patients with nasopharyngeal carcinoma is a recent report by Law *et al.*[6] which demonstrated immunosuppression as measured by depressed lymphocyte response to PHA in malnourished patients. Many clinicians have noted weight loss and malnourishment in patients undergoing irradiation for nasopharyngeal carcinoma.

The immunosuppressive effect we have noted following irradiation of patients with nasopharyngeal carcinoma was probably a result of at least 3 factors. Large volumes of blood were within the treatment fields. While the entire thymus was not in the treatment field the gland received a minimum of approximately 390 rads. Finally, we occasionally observed severe malnour-

ishment secondary to mucositis which required hospitalization during treatment.

The questions which remain unanswered include whether the observed suppression of cellular immunity following irradiation will return to normal and whether suppression will affect the long term prognosis and survival of patients with nasopharyngeal carcinoma.

SUMMARY

Eleven patients treated for nasopharyngeal carcinoma with standard radiation therapy were found to have depressed cell mediated immunity. Post-treatment their total lymphocyte count was decreased by 60 per cent. Eight of 11 patients had depressed T-cell rosettes, and 9 of 10 had abnormal lymphocyte response to PHA. Immunosuppression was probably related to irradiation of large blood volumes, irradiation of the thymus, and malnutrition.

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RADIOTHERAPEUTIC MANAGEMENT OF MALIGNANT MELANOMA OF THE EYE*

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FOR many years enucleation has been the most common treatment for melanoma of the choroid and other malignant tumors of the inner eye. The intent of such treatment is to achieve local control of the disease and to prevent metastases. However, reports in the literature indicate that approximately 50 per cent of these patients at the time of enucleation already have latent distant metastases from which they may die within the next 5 years.[6] A considerable number of these patients are 60 years or older at the time of diagnosis of their malignant eye disease and thus may die of other causes. Some authors[8] believe that enucleation of the eye in a patient 60 years or older will not affect life expectancy, and prefer to delay radical surgery until either useful vision is lost or pain from complicating glaucoma occurs. For these reasons we use conservative means of treatment whenever possible, in an attempt to control the primary tumor and preserve vision of the involved eye.

Unfortunately, melanomas have been described as being generally radioresistant, implying that they are unsuitable for irradiation. However, regarding melanomas of the choroid, there is evidence to the contrary in the literature,[2,5,7] demonstrating the radiosensitivity of these tumors. The selection of patients for treatment with radiation is influenced by the local condition of the tumor and of the involved eye; of secondary importance may be the patient's general health and age. Although histologic confirmation is seldom available in these patients at the time of treatment, the clinical diagnosis can usually be made with a high degree of accuracy by an experienced ophthalmologist.[1]

Most of the lesions in our experience measured from 5 to 15 mm. in diameter, with a height of usually no more than one-third of their diameter at the base. In Stallard's series[7] the extreme values for tumor diameters were 3 and 18 mm. The tumors frequently are of lenticular shape, have a broad base and a height that usually reaches one-third to one-half of the diameter at the base before breaking through Bruch's membrane. Diathermy may be an adequate method of treatment for lesions of relatively early stage with no more than 2 mm. elevation. The site of the lesion within the eye does not seem to significantly alter the results of treatment by irradiation, providing it is located in the choroid. In the opinion of some authors, Bruch's membrane should be intact in order to make the patient eligible for radiation therapy of such a lesion. Sex distribution is nearly equal in most reported series. While the majority of the patients are in the fifth or sixth decade of life, age distribution varies widely, ranging from the second to the ninth decades. Occasionally both eyes may be involved by the tumor.

The purpose of this paper is to report our experience at The Ohio State University Hospitals, the material consisting of 18 evaluable patients with malignant choroid melanoma treated primarily with irradiation.

MATERIAL

Since 1968, 22 patients with primary melanoma of the choroid were treated with irradiation. Of these, 18 patients (Table 1)

* Presented at the Seventy-fifth Annual Meeting of the American Roentgen Ray Society, San Francisco, California, September 24–27, 1974.
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TABLE I

TABULATION OF INDIVIDUAL LESIONS AND RADIATION DOSES GIVEN

Case No.	Patient	Sex	Age	Eye Involved	Diameter of Lesion (mm.)	Date Treated	Ring Diameter	Radon (mc)	Exposure Dose (r)*
1	V.C.	F	56	O.S.	15	4-26-68	15	4.1	6,000
2	C.T.	M	22	O.D.	12	4-30-68	15	4.1	6,000
3	I.D.	F	66	O.S.	13	9- 4-68	15	4.1	6,000
4	K.B.	F	64	O.S.	7	10-18-68	10	3.5	7,500
5	H.B.	F	72	O.S.	13	11-20-68	15	5.3	8,000
6	M.K.	F	54	O.D.	10	7-31-70	12	3.5	6,500
7	W.C.	M	66	O.D.	10	10-20-70	13	3.5	6,900
8	G.M.	F	72	O.S.	15	12-22-70	17	6.4	7,800
9	G.F.	M	76	O.D.	10	4-23-71	12	3.5	6,400
10	C.S.	F	38	O.S.	10	6- 4-71	12	4.3	7,900
11	B.S.	M	56	O.S.	10	6-11-71	13	4.0	6,100
12	L.H.	M	37	O.S.	18	6-24-71	15	4.0	7,500
13	D.C.	F	48	O.D.	15	9- 1-71	16	4.8	7,200
14	J.F.	M	52	O.D.	8	11- 1-71	10	4.5	9,000
15	J.W.	M	54	O.D.	12	4-26-72	14	4.9	8,000
16	M.C.	M	31	O.S.	12	5- 3-72	13	5.0	8,500
17	F.D.	M	56	O.S.	8	8- 3-72	10	3.3	7,400
18	R.H.	F	53	O.D.	9	10- 4-72	12	4.5	8,400

* Dose rounded to the closest 100 r value.

have been followed for sufficient periods of time, so that their treatment results can be analyzed. The other 4, treated more recently, are not included in this report. There were 9 females and 9 males, with ages ranging from 22 to 76 years, and a mean age of 54 years. Sizes of the lesions ranged from 7 to 18 mm. diameter, but most of them were 10 to 15 mm. in size. Two were smaller than 10 mm., and only 1 greater than 15 mm. was observed. All of the lesions were unilateral, with the left eye involved in 10 patients and the right eye in 8 patients. Patient selection for treatment with radiation was based primarily upon tumor size, with the exception of 1 case. If the lesion measured up to 15 mm. in diameter, with an elevation of 2 to 5 mm. and an intact Bruch's membrane, and if vision of the involved eye was not significantly impaired by the tumor, the tumor was irradiated. Patients with very small lesions, up to 5 mm. in diameter and with less than 2 mm. elevation, are preferably treated by transscleral diathermy.[1] When the tumor exceeds the limits of suitability for irradiation or if vision is already lost, enucleation of the involved eye is recommended.

All patients in our series were treated with radon seed implants, with the technique to be described. The "applicator" may be left in place indefinitely. Only in 1 case was the applicator removed, 13 months following implantation, because of suspected progression of disease. So far, there have been no signs of tissue intolerance to the foreign material in any of these patients.

TECHNIQUE

Plesiotherapy, utilizing a modification of a technique first described by Stallard,[7] was employed in all patients of this series. A ring type "applicator," filled with radon seeds, is fashioned out of polyethylene tubing obtained from a No. 20 gauge scalp vein set. The diameter of the ring should be 2 mm. greater than the diameter of the base of the tumor, the tumor size being carefully determined by the examining ophthalmolo-

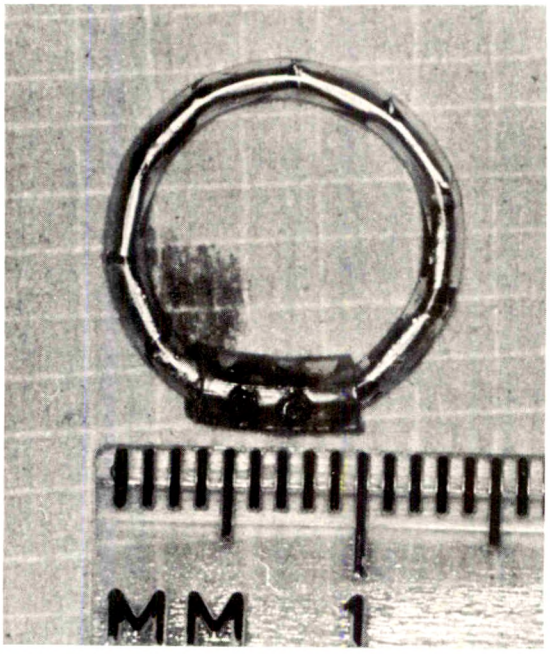

FIG. 1. Applicator ring with radon seeds.

gist prior to the preparation of the applicator. Actually, 2 applicator rings of identical size are prepared for each patient, one containing the radioactive radon seeds and the other to serve as a "dummy" ring to facilitate the surgical procedure. The active applicator is loaded with the number of radon seeds containing the required millicuries of radioactive material. The "dummy" contains an equal number of totally decayed radon seeds. The rings are fashioned by closing the open ends of a piece of tubing as shown in Figure 1. Both the "active" and the "dummy" rings are sterilized over the night preceding the day of the operation, by soaking them in tincture 1:750 of Zephiran chloride. The "active" applicator is carried to the operating room in a lead container for appropriate shielding of personnel. The rings are thoroughly rinsed in sterile normal saline solution prior to their use. The surgical procedure is performed by the ophthalmologist.

SURGICAL PROCEDURE

Under general anesthesia, an incision of the conjunctiva and Tenon's capsule is made in the quadrant overlying the tumor.[4] Extraocular muscles are tenotomized as needed and the sclera overlying the tumor is exposed. By indirect ophthalmoscopy the tumor site is localized and its margins outlined on the scleral surface with nonpenetrating diathermy. Three or four 4-0 white silk sutures are then placed in the sclera with the aid of the "dummy" ring; these will serve to anchor the "active" ring to the sclera. The "active" ring is then placed on the sclera so as to surround the tumor margins and anchored in position by tying the previously placed sutures over it (Fig. 2). The previously tenotomized muscles are then re-attached, followed by the closure of Tenon's capsule and the conjunctiva in layers.

Radiation exposure to the fingers of the operating surgeon has been monitored and found to be approximately 80 mr, which is well within the permissible dose range for an occasional exposure.

During the immediate postoperative period the patient remains hospitalized in a private room, but not confined to his bed, usually for a period of 5 to 7 days in order to satisfy the requirements of prevailing radiation safety regulations. During the first 7 days following the surgical procedure, 72 per cent of the total dose of radiation will be delivered to the tumor site; the remaining 28 per cent of the total dose will be delivered from the seventh day to infinity and probably has little biologic

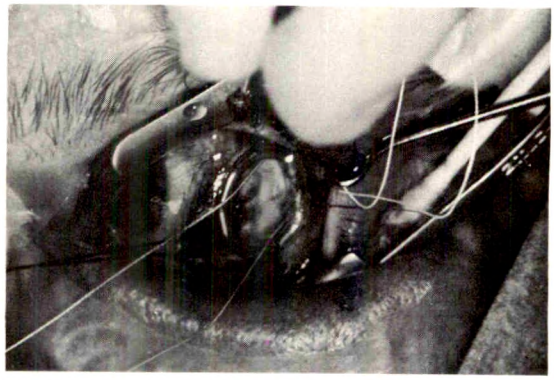

FIG. 2. Applicator ring sutured externally to the sclera of the patient's eye.

effect. The polyethylene ring applicator is left in place indefinitely. Since the material is considered inert, its removal is deemed unnecessary.

DOSIMETRIC CALCULATIONS

In the present series of patients we have used doses in the range of 6,000 to 9,000 r, calculated at a distance of 0.5 cm. from the plane of the ring applicator. The dose is calculated for each individual case, using the Paterson-Parker rules (Manchester system for radium dosage[3]). If, for example, the lesion is 8 mm. in diameter, a ring applicator of 10 mm. diameter will be required. The circumference of such a ring will be 3.14 cm. and since each radon seed measures approximately 4 mm. in length, 8 seeds will be needed to fill the circle. Based on the Paterson-Parker rules, to irradiate an area of 0.8 sq. cm., as in this case, 61 mg./hr. are required for each 1,000 r exposure dose. If a dose of 7,500 r is to be delivered, an exposure equivalent to 457 mg./hr. of radium will be required. Each mc of radon delivers 133 mg./hr. of radium equivalent dose at total decay; therefore, 3.44 mc is the total activity or amount of radon required for this applicator. Since 8 seeds will be used to fill the ring, the strength of each seed should be approximately 0.43 mc at the time of implantation.

RESULTS

All 18 patients included in this report were followed by periodic ophthalmologic examinations and their treatment results as of latest follow-up examination are summarized in Table II. Follow-up time of surviving patients ranged from 18 to 72 months.

The changes observed in these tumors during periodic follow-up examinations indicate that response to radiation is usually slow and that it seldom becomes apparent before 4 to 6 months after treatment.

Table II

ANALYSIS OF TREATMENT RESULTS

Case No.	Patient	Follow-up Period (years)	Local Tumor Response	Complications	Present Status
1	V.C.	5–6	Good	Distant metastases (liver, brain, bone)	Dead
2	C.T.	6	Good	Severe retinal detachment; loss of vision; enucleation	NED
3	I.D.	2–3	Good	Distant metastases (liver)	Dead
4	K.B.	5–6	Good	—	NED
5	H.B.	5–6	Good	—	NED
6	M.K.	3–4	Good	Markedly decreased vision	NED
7	W.C.	3–4	Good	—	NED
8	G.M.	3–4	Good	Markedly decreased vision; vitreous hemorrhage	NED
9	G.F.	3	Good	Moderate loss of vision	NED
10	C.S.	2–3	Poor	Active tumor; retinal detachment; enucleation	NED
11	B.S.	2–3	Poor	Active tumor with partial regression; degenerating eye; refused enucleation	Living with disease
12	L.H.	2–3	None	Active tumor; enucleation	NED
13	D.C.	2–3	None	Active tumor; enucleation	NED
14	J.F.	2–3	Good	Moderate loss of vision; vitreous hemorrhage	NED
15	J.W.	2	None	Active, growing tumor; decreased vision; enucleation	NED
16	M.C.	2	Good	—	NED
17	F.D.	1–2	None	Active tumor; enucleation	NED
18	R.H.	1–2	Good	Slightly decreased vision	NED

The first noticeable favorable change in some cases was pigment dispersion and yellowing around the periphery of the tumor. Flattening and gradual disappearance of the tumor mass was observed in a number of patients only 6 to 8 months after irradiation. Collections of subretinal fluid or retinal detachment, when present, were also slow to regress but appear to precede the regression of the tumor. In some instances, one may see chorioretinal scarring as a late postirradiation effect in patients with good tumor response. Neovascularization of the treated area has not been observed. Postirradiation complications in the involved eye developed in 50 per cent of the patients regardless of local tumor control or not. These have been vitreous hemorrhage, retinal detachment, progressive loss of vision, and even degeneration of the eye. Retinal detachment may not always be exactly a treatment complication, since it is also seen associated with larger tumor masses prior to any therapy. Vitreous hemorrhage tends to resolve with time in most patients. Glaucoma has not been observed in this group of patients. Two patients (Cases 1 and 3) are known to have died from distant metastases 67 and 35 months after treatment, respectively. However, in both, good local control of the primary tumor had been achieved with preservation of vision. Six patients (Cases 2, 10, 12, 13, 15, and 17) underwent subsequent enucleation of the involved eye, either because of treatment complication with loss of vision, as in 1 case, or because of inadequate tumor response. One other patient (Case 11) was advised to have an enucleation because of persistent tumor in the eye, but refused the operation.

The over-all results to date suggest that the main treatment objectives have been achieved in more than 50 per cent of the patients, but further follow-up is necessary to confirm this initial impression. We are encouraged to continue using this treatment method in selected patients, and since no undue morbidity from the treatment has been observed so far, we may in the future increase the dose in some cases because of the slow regression or inadequate response observed in some lesions. We feel that normal tissue tolerance of the eye may permit the use of higher dose levels than those heretofore employed.

CONCLUSIONS

There seems to be little question that, in properly selected patients, melanoma of the eye can respond favorably to treatment by irradiation. A review of 18 patients with melanoma of the choroid, treated with radiation, is presented. The treatment method used requires close cooperation between the ophthalmologist and radiotherapist. Preoperative evaluation of the tumor size is paramount for proper selection of patients who may benefit from this type of treatment. The procedure consists of the surgical implantation of a specially prepared applicator containing radioactive sources (radon seeds), the technique being a modification of that used and described by Stallard.[7] Our results so far are encouraging enough to continue its use. Local control of disease without undue morbidity from the procedure itself and with preservation of useful vision in the involved eye was achieved in 11 of 18 patients. Thus the treatment was locally successful in 61 per cent of all patients, whereas 7 patients (39 per cent) are considered local treatment failures. Only 2 patients have so far died of distant metastases, representing 40 per cent of patients treated 5 years ago. One of these 2 patients survived 67 months and the other 35 months following radiation treatment. Further loss of vision in the treated eye was the most frequent complication, culminating in enucleation in some patients. Of the 6 patients who underwent enucleation, 5 did so because of inadequate local tumor response, and 1 because of complication due to severe retinal detachment.

Of the enucleated eyes, only 1 had a tumor smaller than 10 mm. diameter. The time of enucleation, except for 1 patient, was less than 1 year after irradiation.

In Case 12, one could have anticipated local treatment failure, since the lesion was

actually larger than the diameter of the applicator used. This unfortunately happened because of an inaccurate estimation of the size of the tumor a few weeks before the scheduled implantation procedure. At the time of surgery, the tumor was found to be considerably larger than the applicator prepared for it. The possibility of an unusually rapid growth of this particular tumor cannot be ruled out, of course.

In this series of patients there is no correlation between local treatment failure and the dose of radiation given. Histologically, most patients whose eyes were enucleated had spindle cell B type tumors.

Further use of this technique, with long-term follow-up examination of treated patients, seems justified to better assess the true value of this treatment method.

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THE ROLE OF RADIATION THERAPY IN THE TREATMENT OF PAROTID CARCINOMAS*

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IT has been stated frequently in the surgical literature that there is little role for radiation therapy in the treatment of carcinoma of the parotid.[3,6,8,9,12] A few reports of the value of radiation therapy in the treatment of those malignant tumors have appeared in the radiologic literature, but these have not been widely circulated.[1,11,14]

This report is a retrospective analysis of the material from Ohio State University Hospitals, and attempts to answer the question—"What is the role of radiation therapy in the treatment of carcinoma of the parotid?"

TABLE I

OHIO STATE UNIVERSITY HOSPITALS: CARCINOMA OF PAROTID

Patients reviewed		69
Excluded		
Lost to follow-up	9	
Insufficient histologic or treatment data	5	
No treatment	2	
		16
Total patients available for analysis		53

METHOD

During the period January 1958 through December 1970, 38 patients with carcinoma of the parotid gland alone or in association with carcinoma of other salivary glands were registered in the files of the Division of Radiation Therapy (Table I). An additional 24 patients were registered in the Hospital Tumor Registry which began collecting data in 1962. An additional 7 unlisted patients were kindly pointed out by Dr. Arthur James.

The time period allows for a minimum of 2 years follow-up on all patients. Of the total 69 patients, 9 were lost to follow-up, 5 had insufficient clinical, histologic or treatment data, and 2 were not treated at all or treated elsewhere. Thus, 53 patients remained who were suitable for analysis. Both the hospital and radiation therapy charts were reviewed for pertinent data. Patients who had excisional biopsy only or incomplete excision of tumor were considered to have not been treated with surgery. When patients had definitive surgical treatment, but the surgeon felt that there was tumor remaining behind either grossly or microscopically, the patient was considered to have residual disease. All radiation doses were calculated to tumor depth. Where this was not originally measured, an arbitrary depth of 4 cm. was used. The nominal single dose (NSD) calculation was made according to the original concept of Ellis.[4]

CLINICAL DATA

The average age was 58, with a range from 12 to 89. There were 24 males and 29 females. The most common symptoms were a swelling at the angle of the jaw or in front of the ear with or without pain for periods of 6 months to 10 years.

Definitive treatment by surgery consisted of total parotidectomy with or without hemimandiblectomy and radical neck dissection. In 3 patients with low grade mucoepidermoid carcinoma, only a superficial lobectomy was performed. Treatment by radiation was either with a cesium 137 head and neck unit, cobalt 60 machine or betatron utilizing 15 mev. electrons.

* Presented at the Fifty-sixth Annual Meeting of the American Radium Society, Maui, Hawaii, April 21–25, 1974.
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HISTOLOGIC TYPE

MUCOEPIDERMOID

There were 16 patients with this histologic type. Thirteen patients underwent surgery at OSU Hospitals. Two patients died with disease 10 months and 6 years after treatment. The latter patient had disease extend to base of skull 1½ years after initial surgery. Neither of these patients received radiation therapy.

In 1 patient tumor extended to the neck 11 months after initial surgery and radiation therapy was given for active disease. However, the treatment field was inadequate and the tumor later extended again outside the treated area. He died 3 years after the initial diagnosis. Nine patients were without evidence of disease (NED) 3 to 9 years after surgery (69 per cent). One patient received irradiation for residual tumor postoperatively and was NED 4 years later.

Four patients received radiation therapy after surgery either at OSU or other hospitals. Two were for recurrent disease, and 1 for postoperative residual as mentioned previously. The fourth patient was treated palliatively. Neither patient with recurrent disease was salvaged by irradiation. However, 1 was given what would now be considered an inadequate dose; the 2nd, inadequate coverage by the radiation field.

One patient was treated palliatively by irradiation only and died of disease 10 months later.

Over-all survival without disease for 2 or more years for those with initial treatment at OSU was 10/13 (77 per cent). Adequate irradiation was given in only 1 patient, therefore, no meaningful survival figure for radiation is available. The recurrence (disease occurring in previously treated area) or extension (disease occurring outside the treatment area) rate was 3/13 (23 per cent).

SQUAMOUS CELL CARCINOMA

There were 14 patients with this histologic type. Six patients underwent surgery at OSU Hospitals. One was NED 20 years after surgery, another NED 8 years after surgery and postoperative irradiation for residual disease. One patient who had recurrence 20 months after surgery and had re-excision of disease, is NED 3 years after the initial surgery. Three patients died with the disease within 2 years after surgery. The recurrence rate following surgery was 4/6 (66 per cent).

Four patients considered inoperable were referred for radiation therapy. One patient achieved local control, but died with metastatic disease 2 years later. The other 3 patients died without local control within 1½ years after treatment.

Four patients with recurrent disease after surgery elsewhere received radiation therapy and all died with disease within 3 years after initial therapy. These patients were given doses of radiation designed to relieve symptoms, but not achieve local control.

Over-all survival with or without disease for 2 or more years was 7/14 (50 per cent). For 5 years it was 2/10 (20 per cent). Four patients developed metastatic disease outside the head and neck region (29 per cent).

ADENOCARCINOMA

There were 18 patients with this histologic type. Twelve patients underwent surgery at OSU Hospitals. Only 2 patients were without recurrence with surgery only. An additional 2 patients received postoperative irradiation for residual tumor and were without recurrence 2½ years after irradiation. A 4th patient had 5 recurrences over a 20 year period, all treated by surgical excision, and is currently alive with no apparent disease.

Three patients were treated for recurrences by radiation therapy. Only 1 was salvaged, the other 2 died with disease 3 and 4 years after initial surgery. Four patients died with disease with no further therapy within 26 months of initial surgery.

Four patients were inoperable and received radiation therapy as the primary modality of treatment. One died with disease 5 years after treatment. The other 3

are alive with local control 2, 6, and 11 years after treatment. One of these had extension of disease outside the radiation field and that was also treated and is currently controlled. The other 2 are NED. An additional 2 patients who were treated for residual tumor postoperatively were referred from another institution and are NED at 40 months and 53 months.

The over-all 2 year survival was 15/18 (83 per cent). The over-all 5 year survival was 6/13 (46 per cent). The 5 year disease free survival was 5/13 (38 per cent). The recurrence rate after surgery was 8/12 (66 per cent).

UNDIFFERENTIATED

There were 4 patients with this histologic type. One patient was treated surgically and died within 4 months. The other 3 were deemed inoperable and treated with irradiation. They all died of disease at 22, 26, and 65 months. The latter patient had local control for 4 years before extension of disease to the base of skull.

Over-all 2 year survival was 2/4 (50 per cent) and the 5 year figure was 1/4 (25 per cent).

MALIGNANT MIXED

Only 1 patient had this histologic type. He survived 9 years without recurrence after radical surgery.

TREATMENT

There is no accurate way to compare the modalities of therapy these patients received (Table II). First, most patients were selected for therapy on the basis of extent of disease. Only if patients had residual, recurrent, or inoperable tumors were they referred for radiation therapy. Thus, to compare surgery, surgery and irradiation, and irradiation alone would be very difficult since the groups are not comparable with regard to extent of disease.

However, certain features do become apparent. Since patients with the histologic diagnosis of mucoepidermoid carcinoma have an excellent prognosis with surgery alone (9/11 NED; 81 per cent), the treatment modality of choice appears to be surgery. There was only 1 recurrence after surgery.

Three cases were adequately treated with subtotal parotidectomy and only 1 patient required a neck dissection. The others had no evidence of disease in the neck. The remainder received total parotidectomy with good results. Only 1 patient required sacrifice of the facial nerve. It appears that there is no substitute for experience and judgment by the surgeon.

On the other hand, patients with adenocarcinoma, squamous cell carcinoma and undifferentiated carcinoma did poorly with surgery only. The apparent critical feature

TABLE II

CARCINOMA OF PAROTID: TREATMENT AND SURVIVAL

Surgery Alone (25 Patients)		Surgery and Radiation (16 Patients)		Radiation Alone (12 Patients)	
Adenocarcinoma	7	Adenocarcinoma	7	Adenocarcinoma	4
Squamous cell	5	Squamous cell	5	Squamous cell	4
Mucoepidermoid	11	Mucoepidermoid	4	Mucoepidermoid	1
Undifferentiated	1			Undifferentiated	3
Malignant Mixed	1				
2 Yr. Surv.	18/25		13/16		7/12
3 Yr. Surv.	16/25		13/16		4/10
5 Yr. Surv.	12/18		5/11		3/9

is the timing of radiation therapy. If all patients are considered and therapy is given for recurrent disease only; 1/8 (12 per cent) patients were salvaged. On the other hand 5/6 (83 per cent) patients treated for residual disease immediately postoperatively were NED.

Finally, there were 11 patients who were treated by radiation therapy as the only modality either after biopsy or minimal, partial excision of tumor. Five patients received an adequate dose of radiation with NSD greater than or equal to 1,800 rets.[4] All 5 patients achieved local control of their disease from 2 to 6 years. Six patients received doses less than 1,800 rets and only 1 achieved local control (11 years; 1,670 rets; Table III).

Twenty patients underwent surgery at OSU for other than mucoepidermoid carcinomas (Table IV). Only 4 patients (20 per cent) were free of recurrent disease with surgery only. Three additional patients treated by irradiation for residual disease were NED as well. Thirteen patients, 13/20 (65 per cent), developed recurrent or persistent disease. Three of these were salvaged by multiple surgeries or by radiation therapy (23 per cent). Two others were not controlled by radiation therapy for recurrent disease. Eight patients died with disease within 2 years with no further therapy. There were no recurrences in 4 patients treated immediately postoperatively with radiation therapy.

Table III

CARCINOMA OF PAROTID: DOSE RESPONSE

	NSD Less Than 1,800 Rets	NSD Greater Than 1,800 Rets
Local Control	1/6	5/5

NSD = Nominal single dose.

TIME TO RECURRENCE

Analyzing all 53 patients for the time interval from any treatment to recurrence there were 13 recurrences and 5 extensions after surgery and 4 recurrences and 7 extensions after irradiation (Fig. 1). All but 2 of these recurrences or extensions occurred within 24 months of therapy. One

Table IV

STATUS OF PATIENTS RECEIVING INITIAL TREATMENT AT OSU

Mucoepidermoid		Squamous Cell	
Surgery only—NED	9	Surgery only—NED	1
Radiation therapy for residual—NED	1	Radiation therapy for residual—NED	1
Radiation therapy for recurrence—D c̄ D	1	Surgery for recurrence—NED	1
Surgery only—D c̄ D	2	Surgery only—D c̄ D	3
	13		6
Adenocarcinoma		Undifferentiated Carcinoma	
Surgery only—NED	2	Surgery only—D c̄ D	1
Radiation therapy for residual—NED	2	Radiation therapy only—D c̄ D	3
Surgery for recurrence—(multiple) NED	1		4
Radiation therapy for recurrence—NED	1		
Radiation therapy for recurrence—D c̄ D	2		
Surgery only—D c̄ D	4	Malignant Mixed	
	12	Surgery only	1

Total recurrences after surgery alone = 13/20 = 65%
Recurrences salvaged = 3/13 = 23%
Recurrences after postoperative radiation therapy = 0/4

NED = no evidence of disease. D c̄ D = dead with disease.

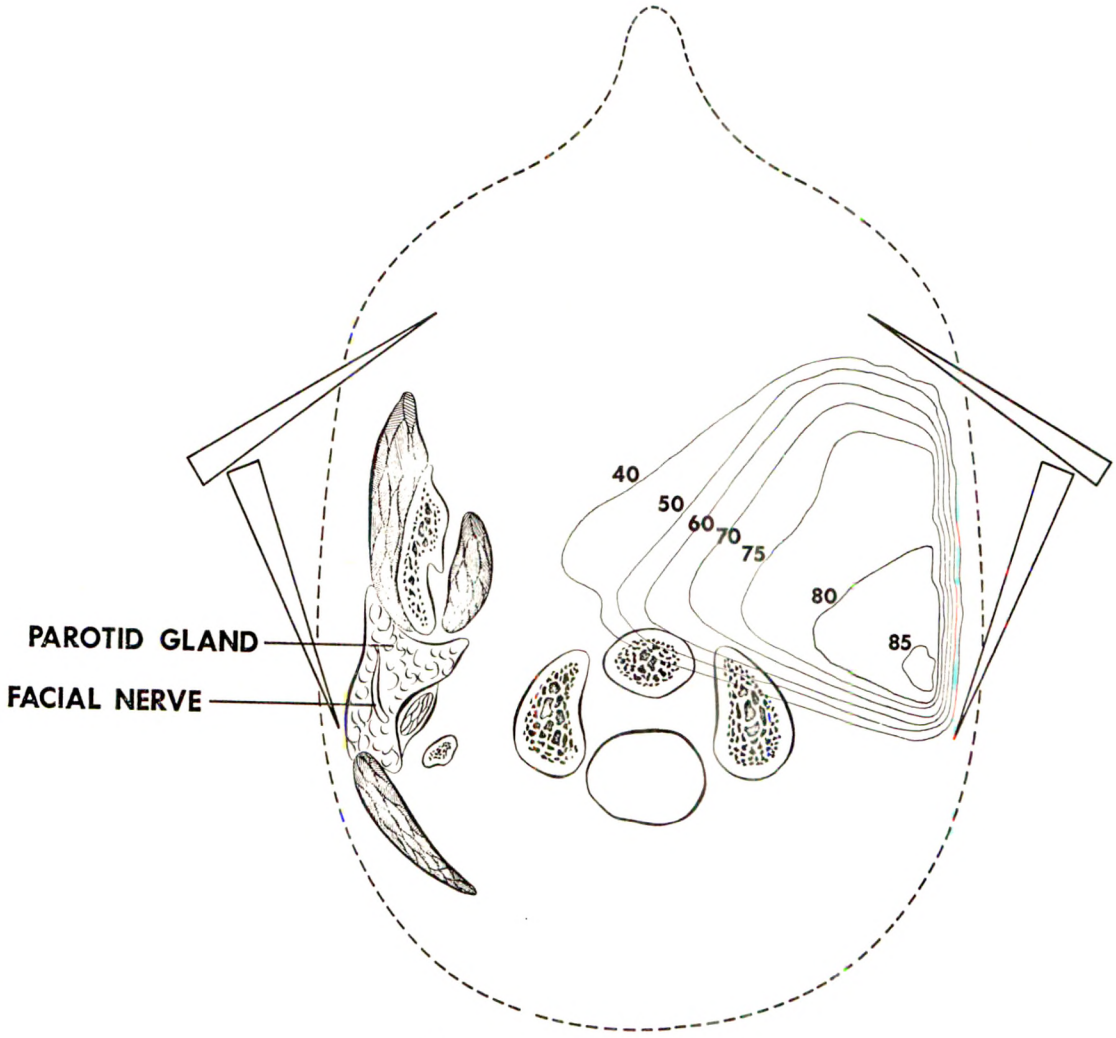

Fig. 1. Dosimetry used.

patient with an adenocarcinoma had 3 recurrences, each approximately 8 years apart, and a 2nd patient had an extension at 46 months after irradiation. Thus, only 4/29 (13 per cent) recurrences or extensions occurred at a greater time interval than 2 years, or 87 per cent of recurrences occurred within the first 2 years.

COMPLICATIONS

Severe complications of radiation were surprisingly uncommon. One patient was left with a painful tongue after an NSD of 2,000 rets. A few patients experienced mild otitis externa, xerostomia, and decreased taste, but these were not serious problems.

EXTENSION OF DISEASE AFTER IRRADIATION

Recurrence and extensions after radiation therapy were usually the result of inadequate dose or field size. Two patients had disease extend to the base of skull despite local control of the primary tumor following irradiation and 8 patients had disease extend to the neck despite local control of the parotid following radiation therapy.

TECHNIQUE

It has been pointed out that the dose necessary for local control of disease is in the range of 1,800 rets of fractionated irradiation (NSD). This means 6,500 rads in

6 weeks minimum tumor dose which can be given in 19 fractions of 225 rads each, treating 5 days per week. The dose should be calculated to at least 4 cm. in depth (Fig. 2). The use of oblique anterior and posterior wedged fields for the parotid bed will tend to preserve the function of the parotid on the opposite side. The lower neck can be adequately treated by an anterior field to a depth of 3 cm. and extending down to the clavicle. It has been shown previously both by Fletcher,[5] and Bagshaw and Thompson[2] that elective radiation therapy of the neck for subclinical squamous cell carcinoma of the head and neck region can eradicate microscopic disease in most patients with only 5,000 rads in 5 weeks.

The fields used in treating the parotid bed should include the base of skull with an adequate margin, since there is a predilection for spread to the stylomastoid foramen and middle cranial fossa in these tumors. In this series, 2 patients, who otherwise might have been cured, had carcinomas extend to the base of skull 2 to 4 years after their irradiation. Another 8 patients developed extension of the disease to the neck, which might have been controlled by adequate coverage of the lower neck initially.

Despite the high rate of development of metastatic disease outside the head and neck region, the radiation therapist should not be deterred from achieving satisfactory local control rates, since metastases may occur late in the course of the disease, and proper radiation therapy may potentially decrease the rate of occurrence of metastatic disease.

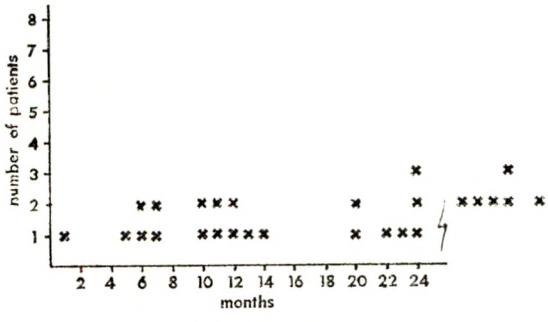

Fig. 2. Time from diagnosis to recurrence of disease.

DISCUSSION

Despite statements to the contrary, there is an important role for radiation therapy in the treatment of malignant tumors of the parotid gland. The present data demonstrate the high recurrence rate following surgery only and the excellent results obtained with radiation therapy immediately following surgery for residual neoplasm. These data suggest strongly that postoperative irradiation should be performed routinely in all patients with squamous cell, adeno- and undifferentiated carcinomas.

King and Fletcher[11] state that histology makes no difference with regard to the role of radiation therapy. However, this study points out the excellent prognosis for the mucoepidermoid carcinomas with surgery alone and, therefore, suggests that radiation therapy should be used only for known residual disease in this histologic type. It is well known that the more poorly differentiated mucoepidermoid carcinomas behave in a more aggressive fashion; therefore, the poorly differentiated lesions probably should receive routine postoperative irradiation.[7]

Jakobisson and Eneroth[10] discuss the radiosensitivity of malignant tumors of the salivary glands with regard to their decrease in size 6 weeks after irradiation. Unfortunately, doses ranged anywhere from 1,200 to 3,500 rads at 3 cm. depth which are probably too low to be of value.

In a recent discussion of parotid tumors Hugo *et al.*[9] state, "Radiation therapy and chemotherapy usually have only palliative effects." However, they also point out that "the major complications of surgery on the parotid gland are facial palsy, auriculotemporal syndrome and *recurrence of tumor*."

The present data suggest that the rate of recurrence, extension or persistence of disease following surgery is high, and that

TABLE V

CARCINOMA OF PAROTID: HISTOLOGY AND SURVIVAL

	2 Yr.	3 Yr.	5 Yr.
Mucoepidermoid	12/16	11/16	9/11
Adenocarcinoma	15/18	13/17	7/14
Squamous cell	7/14	5/12	2/20
Undifferentiated	2/4	1/3	1/3

immediate postoperative irradiation is successful in providing local control and preventing extension of disease to the neck, provided adequate doses and field coverage are used.

Brown *et al.*[3] describe the use of radon seed implants in inoperable or residual tumors after surgery and demonstrate 33 per cent 5 year survival in 36 patients, and state that irradiation is useful and indicated in the treatment of these types of tumors.

Frazell[6] reports 5 year survival rates for a large series of malignant parotid tumors from Memorial Hospital as malignant mixed 55 per cent, mucoepidermoid low grade 96 per cent, high grade 14 per cent, squamous cell carcinoma 36 per cent, adenoid cystic carcinoma 40 per cent, acinic cell carcinoma 82 per cent, solid adenocarcinoma 48 per cent, and undifferentiated tumor 24 per cent.

This series demonstrates similar over-all survival figures (Table v). What is interesting to note is that radiation therapy alone in the squamous cell and adenocarcinomas may lead to 5 year survivals almost as high. This suggests that routine postoperative irradiation may lead to even higher 5 year survivals in these tumors.

The optimum timing for radiation therapy in carcinomas other than well differentiated mucoepidermoid is immediately after surgery rather than waiting to treat clinically evident recurrent disease. Patients treated immediately after surgery for residual disease had a recurrence rate of only 17 per cent. On the other hand, among 20 patients treated with surgery only, initially there was a 65 per cent recurrence rate. Only 23 per cent of recurrences could be salvaged by surgery or irradiation and only 12 per cent of recurrences treated by irradiation only could be salvaged. These data suggest that postoperative radiation therapy in parotid carcinomas should be a routine pr cedure.

The high recurrence rate following surgery only is a common finding.[6,12–14] Although Hollander and Cunningham[8] report a series of surgical patients thought to be "representative of those patients most surgeons are asked to treat," most of their patients had early, occult cancer (only 4 of 30 patients were suspected of having cancer) and favorable histologic diagnosis (acinic cell and mucoepidermoid). They also show a 57 per cent recurrence rate in the neck whether the radical neck specimen was positive or not.

The local control rate (excluding extentions outside the treatment area) in inoperable patients who received *adequate* radiation therapy was 100 per cent in this series and is similar to the observations of King and Fletcher.[11]

SUMMARY

Radiation therapy appears to be useful in postoperative management of patients with parotid gland tumors. Because the local recurrence rate is excessive, postoperative irradiation should be routinely considered for high grade mucoepidermoid carcinomas, all squamous cell, adeno- and undifferentiated carcinomas of the parotid.

Doses should be at least equivalent to 6,500 rads in 6 weeks to 4 cm. depth (or measured tumor depth).

The radiation fields should cover the base of skull and lower neck to prevent extension of the cancer.

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THYMUS-DEPENDENT LYMPHOCYTE LEVELS DURING RADIATION THERAPY FOR BRONCHOGENIC AND ESOPHAGEAL CARCINOMA: CORRELATIONS WITH CLINICAL COURSE IN RESPONDERS AND NONRESPONDERS*

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ALTHOUGH carcinomas of the lung and esophagus often respond to radiation therapy,[10,23] in most instances the cure rates remain low, due not only to persistence of the primary but to the development of regional and distant metastases. In bronchogenic carcinoma, attempts to improve cure rates through a combined radiation and surgical treatment regimen thus far have been unsuccessful;[25,26] in esophageal carcinoma, some trials achieved improved cure rates with combined therapies,[22] but others showed no benefit.[12,14] More distressing are the demonstrations of an increased incidence of distant metastases with the use of combined treatment regimens for these[25] and other malignancies.[10,20,24]

Concomitant with the plateau in cure rates for bronchogenic and esophageal carcinoma with the available modes of therapy and the demonstration of deleterious effects of combined therapy[4,25,26] has been the accumulation of data which may offer an explanation for the failure of combined therapy regimens to achieve greater salvage and data which suggest a new basis for the design of more effective treatment regimens. It is now apparent that immunologic recognition and response to tumor occurs in patients with bronchogenic[1,28] and esophageal carcinomas[30] as in patients with other malignancies.[6,15,21] The concern arises that since patients with bronchogenic carcinoma already have depressed cellular immunity,[3,16] any adjunctive therapy such as radiation or chemotherapy that imposes additional increments on the existing impaired immunity may negate any therapeutic benefits.

The results of clinical treatment programs and investigations of immune responsiveness lead to the hypothesis that preservation of immune competence during treatment of a bronchogenic and esophageal carcinoma with potentially immunosuppressive modalities may be essential for successful tumor control. This study explores the hypothesis in patients with these tumors who were treated with radiation therapy. Using the spontaneous lymphocyte rosette (T cell) test, cellular immunity was assayed serially during and after radiation therapy, and correlations were made between alterations in T cell levels and clinical course after treatment.

MATERIAL AND METHOD

PATIENTS

Fifty-two patients who received radiation therapy for bronchogenic carcinoma were studied. Eighty-one per cent were men. Seventy-two per cent were Caucasian, and the rest were Black. Their mean age was 59 years, with a range of 40 to 79 years. Only patients from who sufficient tumor was removed to permit accurate histologic diagnosis of bronchogenic carcinoma are included. The histologic classification of lung tumors developed by the World Health Organization[29] was used to classify

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the tumors as squamous cell carcinoma (42 per cent), adenocarcinoma (22 per cent), oat cell carcinoma (22 per cent) and undifferentiated carcinoma (14 per cent). Radiation therapy was administered for several reasons: 75 per cent were inoperable (positive mediastinal lymph nodes in 12, positive scalene lymph nodes in 13, and positive carinal biopsy in 3, and bone or brain metastases in 7 patients). Ten per cent were unresectable. Seven per cent had locally recurrent primaries, and 8 per cent were referred shortly after surgical resection either because the tumor was poorly differentiated (2 patients) or because the bronchial stump margin was positive for tumor (3 patients). Because of factors known to alter assays of *in vitro* cellular immunity, patients were excluded if they had received chemotherapy, steroids, were malnourished as manifested by a greater than 20 pound weight loss or a serum albumin of less than 3.2 grams per 100 ml. blood. Patients with synchronously presenting cancers at other sites or who had a history of previous malignancy were excluded. To avoid transitory factors that influence cellular immunity, studies were not conducted in patients who had received general anesthesia within the previous 5 days, blood transfusions within 3 weeks, or who had infections or other acute illnesses. Eight patients initially studied were excluded from this analysis on the basis of these criteria. Another 10 patients studied initially were excluded because serial assays were not obtained.

Twenty patients with esophageal carcinoma were studied. An additional 10 patients studied initially were excluded by the criteria outlined in the preceding paragraph. Seventy-two per cent were men. Forty-eight per cent were Caucasian, the remainder were Black. Their mean age was 62 years with a range of 39 to 82 years. All had sufficient tumor removed to permit an accurate histologic diagnosis of squamous cell carcinoma. The location of the primary was cervical in 10 per cent, middle-third in 60 per cent, and lower-third in 30 per cent. Fifteen patients presented with a primary tumor only, 2 had local recurrence at the site of an esophagogastrostomy suture line, 2 had positive scalene lymph nodes, and one had tumor invasion of the aortic arch.

CONTROL POPULATION

Two hundred and thirty-seven healthy volunteers between the ages of 20 and 80 were studied. Seventy-seven per cent were Caucasian and the rest were Black. Individuals with the history of malignancy or systemic disease or who were taking medications or had acute illnesses were excluded. Eighteen controls were studied repeatedly at intervals throughout the investigation to determine the variation of T cell levels in a normal population.

SPONTANEOUS LYMPHOCYTE ROSETTE ASSAY (T CELL ASSAY)

The method used in this study to evaluate T cell levels in peripheral blood is a modification of the technique for spontaneous rosette formation described by Brain *et al.*,[2] and Wybran. *et al.*[29]

Lymphocytes were separated by Ficoll-Hypaque gradient. Fifteen ml. of peripheral venous blood was drawn into a syringe containing 1,000 units of heparin. The blood was diluted with 30 ml. of Mg^{++} and Ca^{++} free Hanks' BSS and layered over a Ficoll-Hypaque mixture consisting of 10 parts of 33.9 per cent Hypaque (Winthrop Laboratories, New York) and 24 parts of Ficoll 9 per cent (Pharmacia Fine Chemicals, Piscataway, NJ) in a 50 ml. plastic tube (Falcon 2070, Falcon Plastics, Oxnard, CA). The sample was centrifuged for 40 minutes at 400 g at room temperature. The mononuclear cell layer containing approximately 90 per cent lymphocytes and 10 per cent monocytes was pipetted off, washed 3 times in RPMI 1640 culture medium, and adjusted to a final concentration of approximately 2×10^6 cells/ml.

A 0.25 ml. aliquot of the cell suspension was added to a 15 ml. plastic centrifuge tube (No. 58300, Kimble Products, Toledo, OH) containing 0.2 ml. of thrice-washed

1 per cent sheep erythrocytes (NIH Animal Center, Poolesville, MD) and to 0.1 ml. of human pooled AB serum previously heat-inactivated and absorbed against an equal volume of washed sheep erythrocytes for 30 minutes at 4° C. The preparation was incubated for 15 minutes at 37° C., centrifuged at 200 g for 5 minutes, and allowed to stand for at least 1 hour at room temperature before counting.

The cell pellet was gently resuspended with the tip of a Pasteur pipette and one drop of a 1 per cent toluidine blue solution was added to the suspension. An aliquot of this suspension was drawn by capillary action into a Pasteur pipette and transferred onto a hemocytometer. By convention, any lymphocyte with 3 or more adherent sheep erythrocytes was considered a T rosette. The percentage of rosette-forming lymphocytes was evaluated under a light microscope at 640× magnification. All samples were done in triplicate and at least 200 cells per sample were counted. Results were expressed as the mean of the 3 samples. All samples throughout the study were read by the same individual without knowledge of the patient's identity.

The "T cell level" was defined as the number of T cells per cu. mm., calculated by the formula "number of T cells = total leukocyte count × per cent lymphocytes × per cent T cells." Total and differential leukocyte counts were obtained on each sample. All total leukocyte counts were done on a Coulter counter (Model ZBI, Coulter Electronics, Hialeah, FL). All differential leukocyte counts were done by the same individual throughout the study without knowledge of the patient's identity.

RADIATION THERAPY

All patients received supervoltage radiation therapy from either a 4 or a 6 MV linear accelerator. Most bronchogenic carcinomas were treated with 5,000 rads to the mid-chest depth in 25 treatments over 5 weeks, through opposing anterior and posterior portals which included the mediastinum from above the suprasternal notch and down to the 4th intercostal space and across the midline to the contralateral sternal border. The exceptions included 1 patient, whose fractional dose was 180 instead of 200 rads, and 2 who received concurrent whole brain irradiation of 1,800 and 3,000 rads during irradiation of the chest. The portals averaged 10×12 cm. in size except in patients with positive scalene lymph nodes, who had larger than average portals to encompass the involved regions. Eight patients who received irradiation for bronchogenic carcinoma metastases through small, non-mediastinal portals, and were not receiving concurrent mediastinal irradiation, were studied (Fig. 7). The esophageal carcinomas were treated with 5,000 rads in 25 treatments over 5 weeks through opposing anterior and posterior mediastinal portals which averaged 6×15 cm. in size.

STATISTICAL METHODS

The Student T test was used to determine significant differences between the mean T cell levels of the responders and the nonresponders to radiation therapy during and after irradiation, calculating d.f. as n_1+n_2-2. Chi square analysis was used to determine significance between the difference in patient composition between the responder and nonresponder groups.

RESULTS

T CELL LEVELS IN CONTROLS

When analyzed by age distribution, there was no significant difference in the mean T cell levels of the individuals in each decade. The T cell levels of Caucasians and Blacks did not differ significantly ($p > .1$). The mean T cell level for the control population was 1,482, with a standard deviation of 522 and standard error of 34. Serial determinations of T cell levels in 18 normals studied over a 9 month period showed a variation of ±12 per cent.

T CELL LEVELS DURING RADIATION THERAPY

Thirty-seven patients with bronchogenic carcinoma had serial determinations of T cell levels commencing with or shortly after

the beginning of radiation therapy. In all, T cell levels fell precipitously during the course of therapy. In 11 patients, the T cell levels either prior to treatment or at an interval before a cumulative dose of 4,000 rads declined to <400. Ten of these patients developed metastases or died of metastases at an average of 2 months after therapy (Fig. 2), but the remaining patient shows no sign of recurrent tumor at 6 months after treatment (Fig. 1). Of 3 patients with esophageal carcinoma with T cell levels <400 during therapy, 1 died before completion of therapy, another developed metastases 3 months later, and a third completed therapy less than 1 month prior to this evaluation.

T CELL LEVELS AFTER RADIATION THERAPY

Responders. Sixteen patients with bronchogenic carcinoma completed radiation therapy and were without evidence of recurrence or metastases at an average of 4 months after therapy (range 1–6 months). In all except 1, T cell levels were abruptly increased at 1 month after completion of radiation therapy. In the patients who have been followed for several months after completion of therapy the T cell levels have stabilized at levels below that prior to treatment but significantly higher than the levels at completion of therapy (Fig. 1).

Nonresponders. Among patients with bronchogenic carcinoma who survived beyond the post-treatment interval, 14 have developed metastases or died of metastases at an average of 2.5 months after completion of therapy. A plot of T cell levels of these patients during and after radiation therapy shows that in all except 2, the decline in T cell levels sustained during radiation therapy persisted in the interval after therapy. In one patient there was an abrupt rise after therapy that was followed by a decline to <400. The other patient has been followed for less than 1 month after therapy (Fig. 2). Seven patients with esophageal carcinoma survived radiation

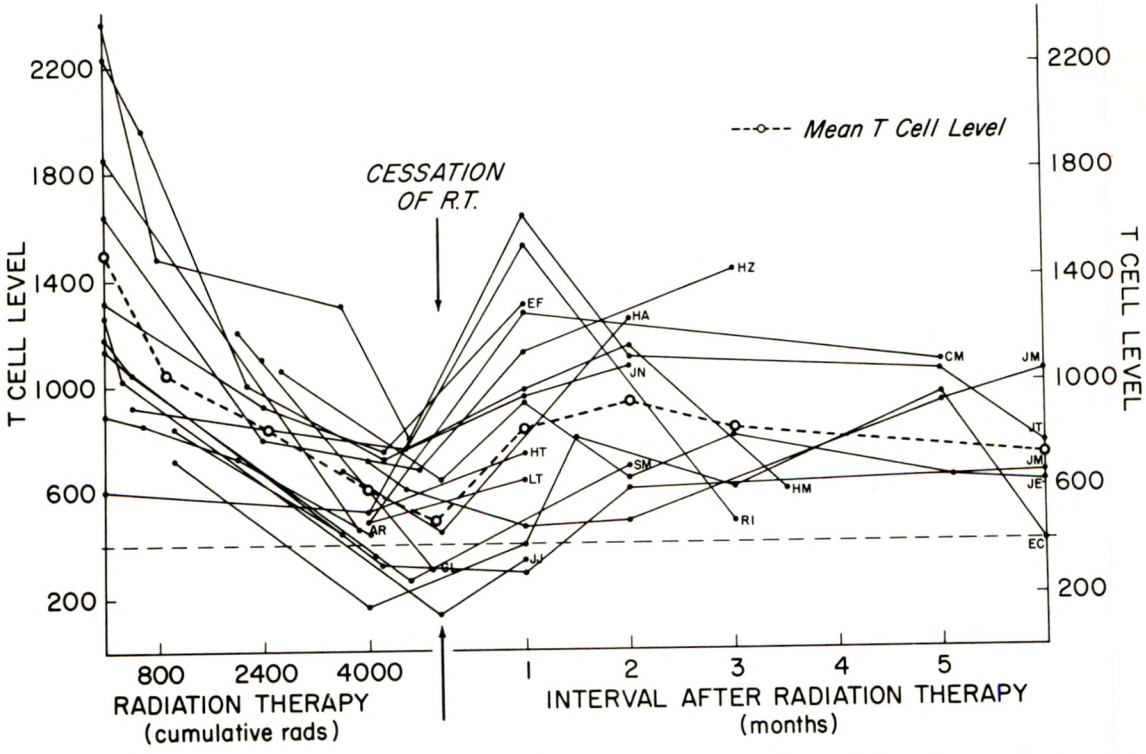

Fig. 1. T cell levels in patients with bronchogenic carcinoma treated with radiation therapy: Responders.

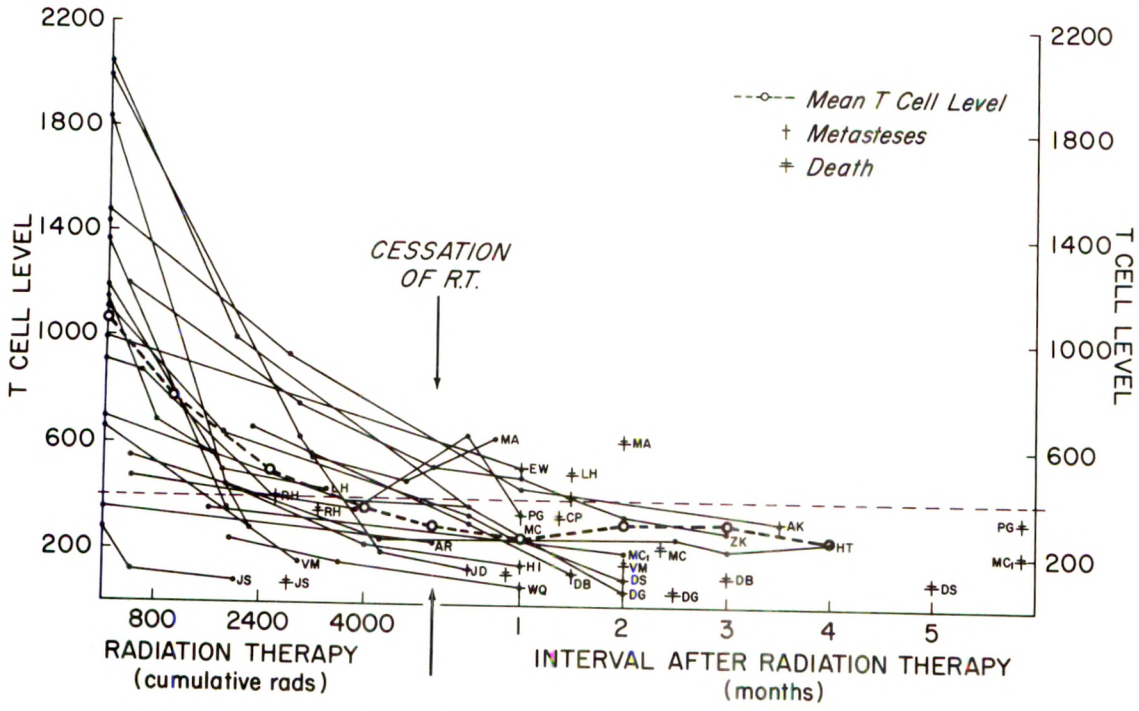

Fig. 2. T cell levels in patients with bronchogenic carcinoma treated with radiation therapy: Nonresponders.

therapy, but all died within 6 months. The T cell levels of 4 of these patients rose slightly after completion of therapy but in the 3 who have had subsequent determinations the levels declined to <400 (Fig. 4).

Mean T cell levels in responders and nonresponders

Comparison of the mean T cell levels of the patients with bronchogenic carcinoma surviving at the time of evaluation (responders) with that of the mean T cell levels of patients who have developed metastases or died (non-responders) shows significantly higher T cell levels in responders throughout the period of radiation therapy. At 1 month after completion of radiation therapy, the mean T cell levels of the responders increased abruptly and persisted at this higher level. By contrast, the mean T cell levels of the nonresponders persisted at <400 after completion of therapy for the entire (4 month) post-treatment interval monitored (Fig. 3). The difference in mean T cell levels of responders and nonresponders during the post-treatment period was highly significant ($p < .0001$).

T cell levels in patients first studied after radiation therapy

Six patients with bronchogenic carcinoma whose evaluation began after completion of radiation therapy had steadily declining T cell levels and all developed metastases and were dead at an average of 8 months after radiation therapy. In all, the development of clinically apparent metastases was associated with or preceded by a decline in T cell levels. Similarly, 9 patients with esophageal carcinoma first studied after radiation therapy include 5 who have developed metastases; in 4 with serial determinations of T cell levels prior to appearance of metastases, a decline in the levels preceded or was associated with the appearance of metastases. Three patients with rising T cell levels remain free of clinically apparent tumor.

T cell levels during irradiation of metastases

Eight patients with bronchogenic carci-

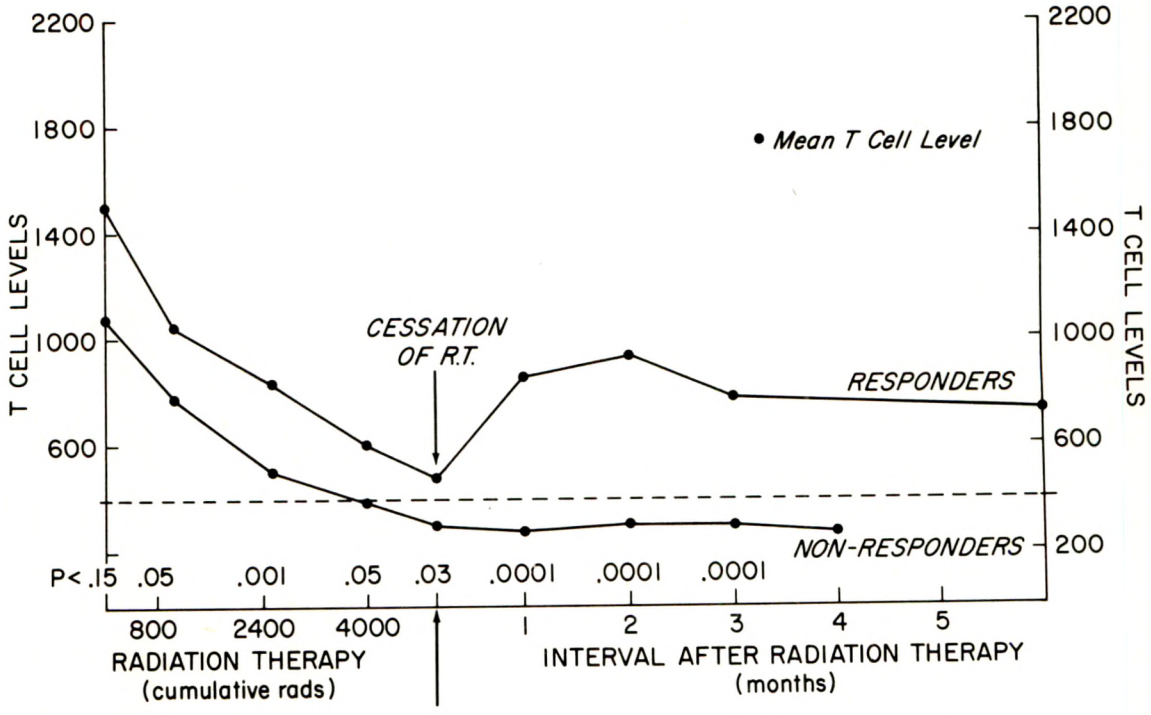

Fig. 3. Mean T cell levels in patients with bronchogenic carcinoma treated with radiation therapy: Comparison of responders and nonresponders.

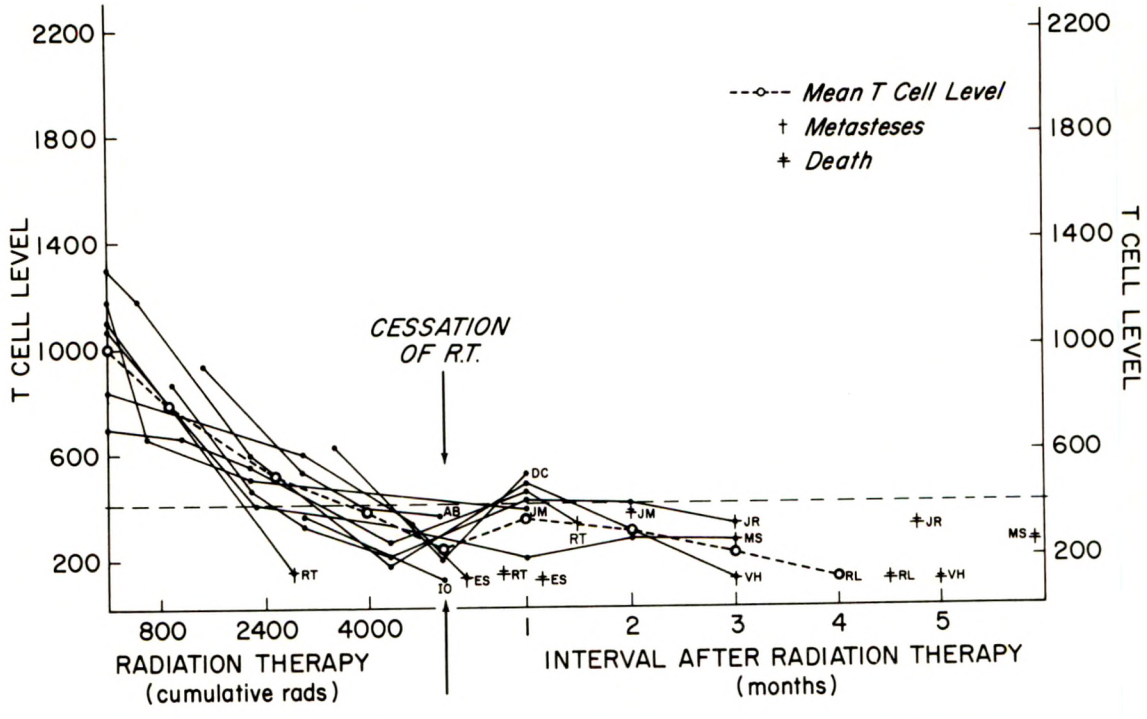

Fig. 4. T cell levels in patients with esophageal carcinoma treated with radiation therapy.

TABLE I

COMPARISON OF HISTOLOGY AND EXTENT OF TUMOR IN RESPONDER AND NONRESPONDER PATIENT GROUPS WITH BRONCHOGENIC CARCINOMA

	Responders	Nonresponders	
Number of Patients	16	21	
	Per cent of Totals		*Statistical Difference**
Tumor Histology			
Squamous cell carcinoma	40	43	N.S.
Adenocarcinoma	24	19	N.S.
Oat cell carcinoma	18	24	N.S.
Undifferentiated carcinoma	18	14	N.S.
Extent of Tumor			
Resectable	40	5	$p<.05$
Unresectable	18	19	N.S.
Metastases present†	42	76	$p<.05$

* Statistical difference by Chi Square analysis.
† Metastases to mediastinal and supraclavicular lymph nodes.
N.S.: Not significantly different.

noma received radiation therapy to nonmediastinal portals for treatment of metastases. Only 2 were treated with less than 4,000 rads. In 7 of the 8 patients, T cell levels remained stable throughout the radiation interval, in contrast to the marked decline in T cell levels that occurred in patients treated with irradiation to the primary. In 1 patient treated *via* a large abdominal portal, however, there was a precipitous fall in T cell levels during the administration of 4,000 rads (Fig. 7).

CORRELATION OF HISTOLOGY AND EXTENT OF TUMOR

The 16 responders and 21 nonresponders with bronchogenic carcinoma had similar incidences of the 4 histologic types of tumors represented. Subdivision of the 2 groups according to the extent of tumor present shows that the responders had a statistically higher incidence of resectable tumors (40 per cent) than the nonresponders (5 per cent) ($p<.05$). The incidence of unresectable tumors was similar in the 2 groups. Although the incidence among responders of patients with metastases was high (42 per cent) it was statistically lower ($p<.05$) than the incidence among nonresponders (76 per cent) (Table 1).

DISCUSSION

The correlations between T cell levels and clinical course of the patients studied in this report show that data derived with this assay give clinically useful insight into the cellular immune competence of patients with bronchogenic and esophageal carcinoma. T cell levels at 3 distinct time intervals—during radiation therapy, immediately after completion of therapy, and serially in the period after treatment—correlated with subsequent clinical course and survival after therapy.

That 91 per cent of patients with bronchogenic carcinoma whose T cell levels were <400 at any period prior to receiving a cumulative radiation dose of 4,000 rads had a mean survival of only 2 months after completion of therapy appears to delineate a patient group in whom adjuvant therapy, *e.g.*, chemotherapy or immunotherapy, will be required for increased survival. Since the ultimate poor prognosis in this patient group was associated with low T cell levels determined early in the course of radiation therapy, the correlations may provide a basis for the early institution of adjuvant therapy prior to the clinical manifestation of metastases.

A significant finding in patients with bronchogenic and esophageal carcinoma studied during and immediately after radiation therapy was the abrupt rise in T cell levels at one month after completion of therapy in responders (Fig. 1), that contrasted sharply with persisting low levels or a decline in T cell levels in nonresponders (Fig. 2; and 4). Cheema and Hersh[7] found that a similar early "rebound" in *in vitro* lymphocyte reactivity to phytohemagglutinin after a course of palliative chemotherapy in patients with solid tumors correlated with relatively long remission intervals, and O'Toole *et al.*[21] showed a relation between increased *in vitro* lymphocyte cytotoxicity against tumor cells and a

therapeutic effect of irradiation for carcinoma of the urinary bladder. Previous studies[1,27] of the effect on *in vitro* lymphocyte reactivity to phytohemagglutinin of radiation therapy for carcinoma of the lung did not include assay of lymphocyte reactivity during the early post-treatment period, although partial recovery of reactivity was demonstrated in many patients at later intervals. In this study, the difference in the tumor-free interval between the responders (no evidence of metastases at a mean of 4 months post-therapy) compared to the nonresponders (metastases developed at a mean of 2.5 months post-therapy) gives importance to the monitoring of T cell levels during the first month after radiation therapy (Fig. 3). Further importance of the T cell changes during this interval is given by the demonstration that the correlations with prognosis were independent of the histologic type of tumor treated and that the assay discriminated between responders and nonresponders even in patients who had regional metastases at the time of treatment (Table 1). Clinical application of these findings would allow the selection of patients for early administration of adjuvant therapy who would have a relatively short survival after treatment with radiation therapy alone.

In patients with bronchogenic and esophageal carcinoma first studied after radiation therapy, correlations with T cell levels and clinical course showed that successive falls in T cell levels coincided with or heralded the later appearance of clinically-manifest tumor recurrence (Fig. 5; and 6). These correlations parallel previous associations in patients with bronchogenic carcinoma and a variety of other tumors of impaired cellular immune competence measured by *in vitro* lymphocyte reactivity[3,6,8] or skin testing with dinitrochlorobenzene and delayed hypersensitivity recall antigens,[3,5,9,28] with extent of tumor and response to treatment. In contrast to these previous studies which correlated immune reactivity and prognosis of *patient groups*, the correlations between fluctuations in T cell levels and clinical course of individual patients in this study, because of the sensitivity of the assay, show that frequent determination of T cell levels offers a means

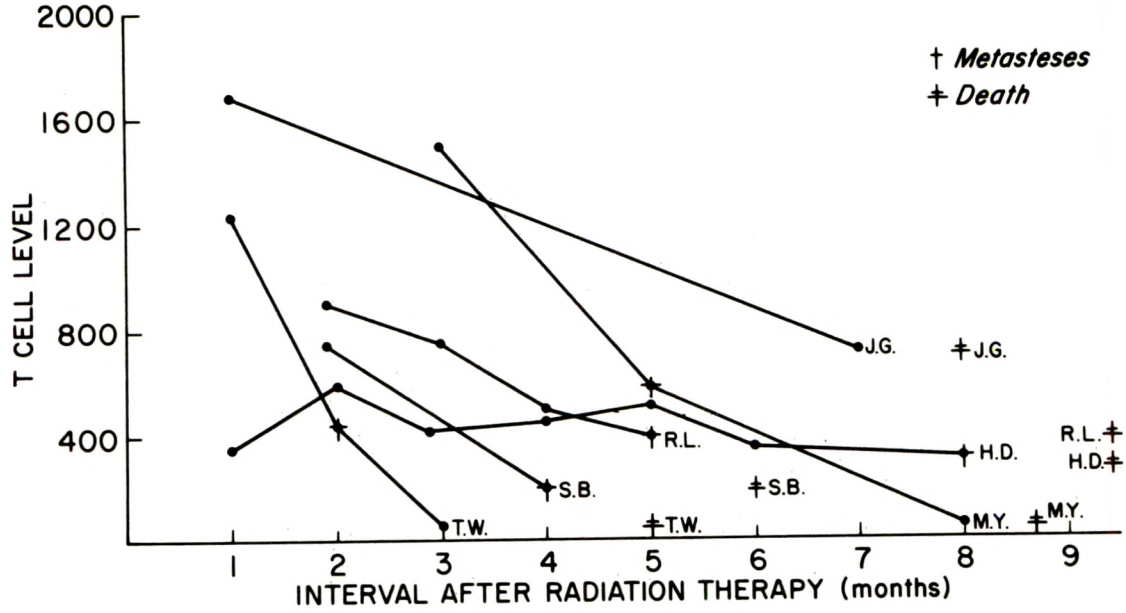

Fig. 5. T cell levels in patients with bronchogenic carcinoma treated with radiation therapy: Long-term responders.

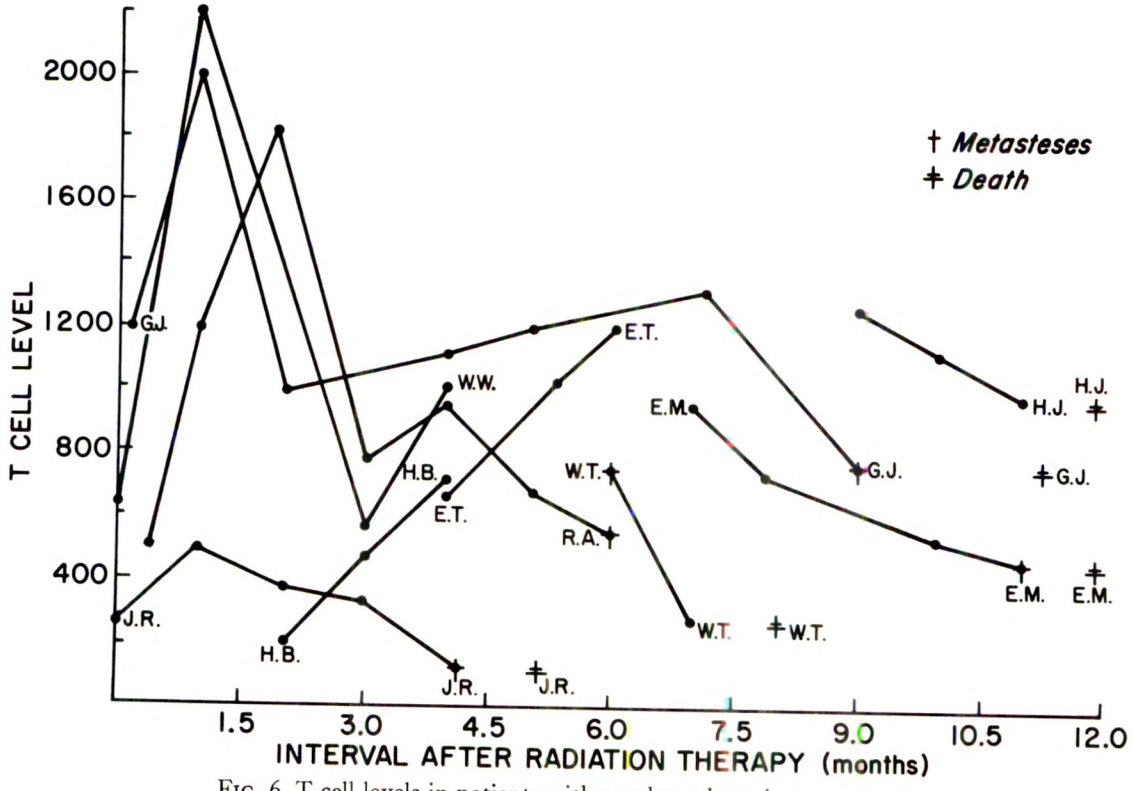

FIG. 6. T cell levels in patients with esophageal carcinoma treated with radiation therapy: Long-term responders.

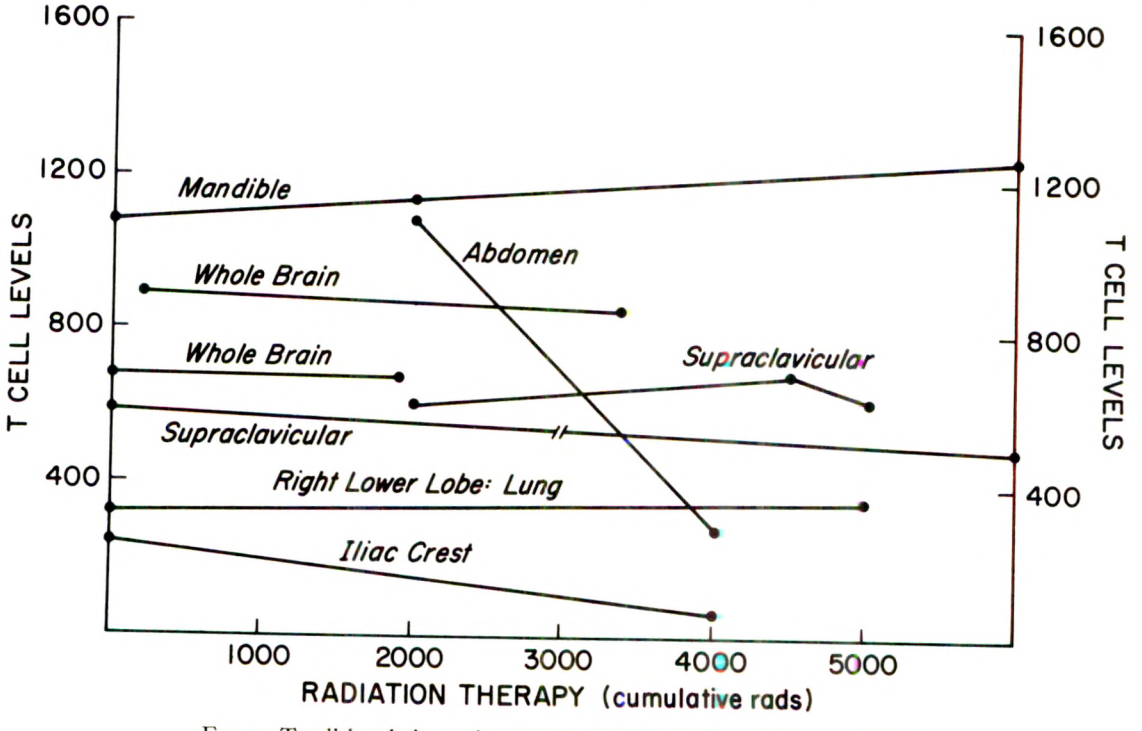

FIG. 7. T cell levels in patients with bronchogenic carcinoma treated with radiation to nonmediastinal portals.

of predicting the course of *individual patients*. Monitoring of T cell levels serially in the post-treatment period would, therefore, afford the clinician an opportunity to institute adjuvant therapy prior to the appearance of recurrence, at a time when a greater therapeutic effect of the adjuvant therapy may be achieved. Since the site of recurrence would not be apparent in these patients, systemic therapy would be utilized, *i.e.*, chemotherapy or immunotherapy.

Since previous studies suggesting that cellular immunity is depressed following radiation therapy for bronchogenic carcinoma were not longitudinal in design, they did not exclude the possibility that their patients had occult metastases present at the particular post-therapy time interval they were studied.[1,27] Such a metastasis could itself depress the cellular immunity. In the present longitudinal study only patients proven over time to be tumor free were included in the "responder" group. The decrease in T cells during radiation therapy observed in this responder group is, therefore, an accurate reflection of radiation effect.

The probable causes of the decrease in T cell levels during radiation therapy for bronchogenic or esophageal carcinoma can be inferred from the study of T cell levels during irradiation delivered to non-mediastinal portals (Fig. 7). The stable T cell levels in 7 of 8 of the patients show that the major contributor to the decline in T cell levels during irradiation of the primary was probably secondary to irradiation of the thymus or lymphocytes circulating in the heart and great blood vessels encompassed by the portals. The fall in T cell levels in 1 patient who received radiation therapy *via* an abdominal portal (Fig. 7) further documents the suppressive effect on circulating lymphocytes of radiation therapy given *via* portals that encompass large blood vessels or major portions of red bone marrow.[13,18] That this effect of radiation therapy is at least partially transient is shown by the rise in T cell levels after completion of therapy of the primary in the responders (Fig. 1). This rise also gives evidence that the persisting low T cell levels in nonresponders (Fig. 2; and 4) are due primarily to continued tumor growth. The long-term effects of radiation therapy on cellular immunity, on the other hand, cannot be deduced from this study, since most of the patients were treated primarily for palliation.

Extensive trials of presently available modalities for the treatment of bronchogenic and esophageal carcinoma have thus far yielded low salvage rates. In patients with bronchogenic carcinoma, utilization of treatment modalities such as radiation therapy or chemotherapy combined with surgical resection have failed to improve these rates, and in some instances have actually yielded lower cure rates than that achieved with surgical resection alone.[4,25,26] In patients with esophageal carcinoma, the addition of preoperative radiation therapy has improved cure rates after surgical resection in some series,[19,22] but not in others.[12,14] Thus, increases in the cure rates of these tumors must be sought by development of new treatments or a new basis for the selection and administration of presently available treatments. Furthermore, the demonstrations of increased incidences of distant metastases in patients with a variety of solid tumors treated with radiation therapy as an adjuvant to surgical resection[10,20,24,25] illustrate the need for a means of predicting the relative beneficial and deleterious effects of radiation therapy in individual cancer patients. The results of this study appear to indicate an approach to the solution of some of these present impasses. For instance, the correlations in this study of relatively short survival intervals in patients with T cell levels <400 prior to or during radiation therapy may serve as criteria for the interdiction or cessation of radiation therapy or the addition of agents that stimulate immune reactivity. In patients receiving radiation therapy as a preoperative adjuvant, a situation most applicable for esophageal carcinoma, per-

sisting low T cell levels after completion of therapy may indicate the presence of clinically occult metastases; here the assay may thus serve as a basis for selection of chemotherapy as a sequel to irradiation rather than an attempt at surgical resection.

CONCLUSION

The major conclusion from this study, therefore, is that in patients with bronchogenic and esophageal carcinoma, quantitation of cellular immunity by assay of T cell levels and serial determination of the effects of therapy on T cell levels may offer a rational basis for the selection of treatment modalities and the early determination of the effects of therapy. The increasing numbers of clinical protocols utilizing radiation therapy in combination with other modalities in an attempt to improve the cure rates of these tumors warrant an early determination of the usefulness of assay of T cell levels in the design and monitoring of these regimens.

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METASTATIC INVOLVEMENT OF THE STOMACH SECONDARY TO BREAST CARCINOMA*

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SECONDARY neoplastic involvement of the stomach is most commonly the result of direct spread from a contiguous neoplasm such as carcinoma of the pancreas or from a non-contiguous tumor such as carcinoma of the transverse colon which may spread to the stomach *via* the gastrocolic ligament. The roentgenographic changes produced by direct extension depend upon the site of the primary neoplasm and the degree of gastric invasion. These changes are well-known and fully described in the literature.

Involvement of the stomach by blood-borne metastatic malignancy is relatively uncommon. The primary neoplasms which most frequently metastasize to the stomach via the blood are malignant melanoma and carcinoma of the breast.[10] The true incidence of gastric metastases secondary to carcinoma of the breast is difficult to ascertain from autopsy studies, being variously reported as 2 to 15 per cent.[7] This variability is largely due to the inclusion by some authors of cases with peritoneal carcinomatosis in which gastric involvement is limited to serosal implants only.[1] If cases are restricted to those with involvement of all or several layers of the gastric wall such as the muscularis, submucosa and mucosa, a more valid estimate of the incidence of gastric metastases may be obtained. Some of the larger series reported in the literature are indicated in Table I.

The present paper is essentially concerned with a description of the roentgenologic findings associated with gastric metastases secondary to carcinoma of the breast and is based upon the author's experience with 9 such cases. Five illustrative examples have been selected from this group.

TABLE I

MATERIAL FROM THE LITERATURE

Authors	No. of Cases of Breast Carcinoma	No. of Cases with Gastric Metastases	Percentage
Asch *et al.*[2]	337	20	6.0
Choi *et al.*[4]	341	28	8.1
Graham and Goldman[5]	75	10	13.3
Hartmann and Sherlock[6]	204	31	15.1

REPORT OF CASES

CASE 1. A 53 year old female underwent a right mastectomy for carcinoma of the right breast in 1966 and a left mastectomy for carcinoma of the left breast in 1968. In January 1970 osteoblastic bone metastases were noted in the lumbar spine, pelvis, ribs and scapulae. In September 1970 the patient was admitted to hospital with a history of anorexia, postprandial epigastric discomfort and fullness of 6 to 8 weeks' duration, and a 20 lb. weight loss. Laboratory data revealed a microcytic anemia, Guaiac positive stools and a hematocrit of 30 per cent. An upper gastrointestinal series revealed a diffuse narrowing of the lumen of the stomach with rigidity and absent peristalsis (Fig. 1*A*). A localized collection of barium on the lesser curve aspect of the body of the stomach was thought to represent a large ulcer crater. Osteoblastic bone metastases were noted in the lumbar vertebrae. Following a course of radiation therapy (3,000 r) to the stomach and chemotherapy, there was fairly good symptomatic relief. A repeat upper gastrointestinal examination 10 months later revealed no significant change in the roentgen appearances. A diffuse linitis plastica appearance with a large "ulcer crater" on the lesser curve aspect of the body of the stomach was again demonstrated (Fig. 1*B*). The patient expired shortly after

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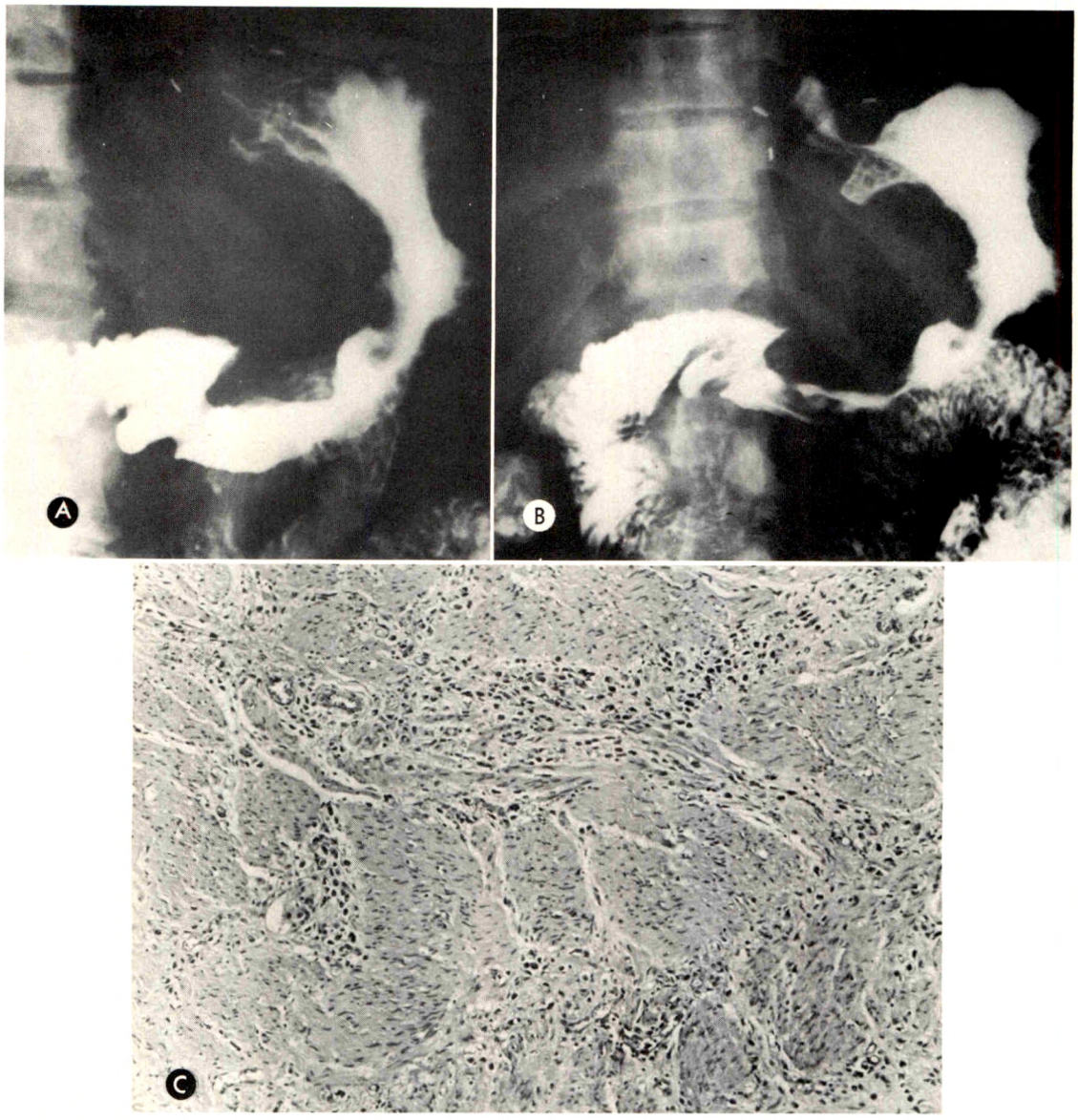

Fig. 1. Case 1. (*A*) Note diffuse, rigid narrowing of the entire stomach with slight nodularity of its contour and localized collection of barium on lesser curve aspect of body of stomach thought to represent a large ulcer crater. (Surgical clips and pyloroduodenal deformity are due to previous vagotomy and pyloroplasty for duodenal ulcer.) Osteoblastic metastases are present in the lumbar vertebrae. (*B*) Repeat upper gastrointestinal examination 10 months later reveals no essential change in the diffuse linitis plastica appearance or in the apparent "ulcer" on the lesser curve aspect of the body of the stomach. (*C*) Photomicrograph showing diffuse infiltration of the muscularis by carcinoma cells which were identical in appearance to those of the primary breast tumor.

this examination and autopsy confirmed the presence of disseminated breast carcinoma with gross infiltration of the wall of the stomach, predominantly the muscularis (Fig. 1*C*) and submucosa by tumor cells identical to those seen in the primary breast lesions. No gross mucosal ulceration was detected although there was marked redundancy of the mucosa associated with the submucosal infiltration. In addition to marked gastric involvement there were widespread peritoneal deposits as well as metastases in the bones and liver.

Case II. An 81 year old female presented with a large firm mass in the left breast associated with axillary lymphadenopathy, skin nodules on her abdomen and back, hepatomegaly and ascites. She complained of epigastric distress and intermittent vomiting of 3 months' duration and dysphagia of 3 weeks' duration. An upper gastrointestinal tract examination revealed a large hiatus hernia associated with gastroesophageal reflux. There was a diffuse narrowing of the stomach with nodularity of its contour, especially in the region of the body (Fig. 2, *A* and *B*), associated with rigidity and diminished peristalsis. No discrete ulcerations were detected and the duodenum was normal apart from a large diverticulum arising from its 3rd portion. One week after admission to hospital the patient suffered an acute myocardial infarction with pulmonary edema and expired. Autopsy examination revealed a 5×5×8 cm. infiltrating carcinoma of the left breast with subcutaneous metastases and skin nodules. There was marked thickening of the gastric wall due to infiltration by tumor. Histologic examination revealed anaplastic carcinoma identical in appearance to the primary breast tumor. Infiltration was most marked in the submucosa and muscularis (Fig. 2*C*), but small foci of cancer cells were also noted in the mucosa. In addition to involvement of the stomach there were metastatic deposits in the peritoneum, omentum, liver, kidneys and adrenals.

Case III. A 78 year old female was admitted to hospital complaining of nausea, vomiting and epigastric distress of approximately 3 eekws' duration. Metastatic carcinoma of the right breast had been diagnosed 2 years previously and was treated with radiation therapy, hormones, chemotherapy and prednisone for hypercalcemia. A chest roentgenogram showed osteolytic and osteoblastic metastases in the ribs, but no pulmonary deposits. An upper gastrointestinal series revealed narrowing and rigidity of the pyloric antrum and distal portion of the body of the stomach with a fine nodularity of the greater curve aspect of the antrum (Fig. 3*A*). The gastric mucosa appeared intact (Fig. 3*B*), but there was some fixation and spiculation of the mucosal folds on the superior aspect of the 3rd and 4th portions of the duodenum suggesting serosal implantation at this site (Fig. 3*A*). Subsequent autopsy examination confirmed the presence of disseminated breast carcinoma with metastases in the ribs, heart, kidneys and skin. There was diffuse tumor infiltration of the wall of the body and antrum of the stomach producing gross thickening of the wall, especially in the region of the pyloric antrum. Histologic examination revealed tumor infiltration of the serosa, muscularis and submucosa with the most marked infiltration in the subserosal region (Fig. 3*C*). The peritoneum was studded with small metastatic nodules and approximately 500–1,000 cc. of serous fluid was present in the peritoneal cavity. Large serosal implants were noted on the distal duodenum. Histologic appearances of the tumor in the breast and stomach wall were identical.

Case IV. A 51 year old female with a previous history of left radical mastectomy for an infiltrating ductal carcinoma was admitted to hospital with acute cholecystitis and underwent a cholecystectomy. At the time of surgery numerous peritoneal metastases and firm thickening of the prepyloric region of the stomach were detected. Histologic examination of a peritoneal deposit revealed a poorly differentiated adenocarcinoma identical in appearance to the breast tumor previously resected. Approximately 1 year following the cholecystectomy the patient was readmitted to the hospital complaining of intermittent epigastric pain, nausea and vomiting of 3 weeks' duration. An upper gastrointestinal tract examination revealed a localized narrowing of the prepyloric region of the stomach associated with partial gastric outlet obstruction (Fig. 4*A*). The mucosa in the region of the rigid, narrowed segment appeared intact (Fig. 4*B*). Following a period of nasogastric suction there was marked symptomatic improvement and the patient remained relatively well for approximately 18 months at which time she presented with epigastric distress, vomiting and Guaiac positive stools. An upper gastrointestinal examination now revealed at least 2 large ulcer craters in the region of the narrowed prepyloric segment (Fig. 4, *C–E*). There was no evidence of significant gastric outlet obstruction and treatment consisted of chemotherapy. However, response to therapy was relatively poor and following a progressive downhill course the patient expired. No autopsy was obtained.

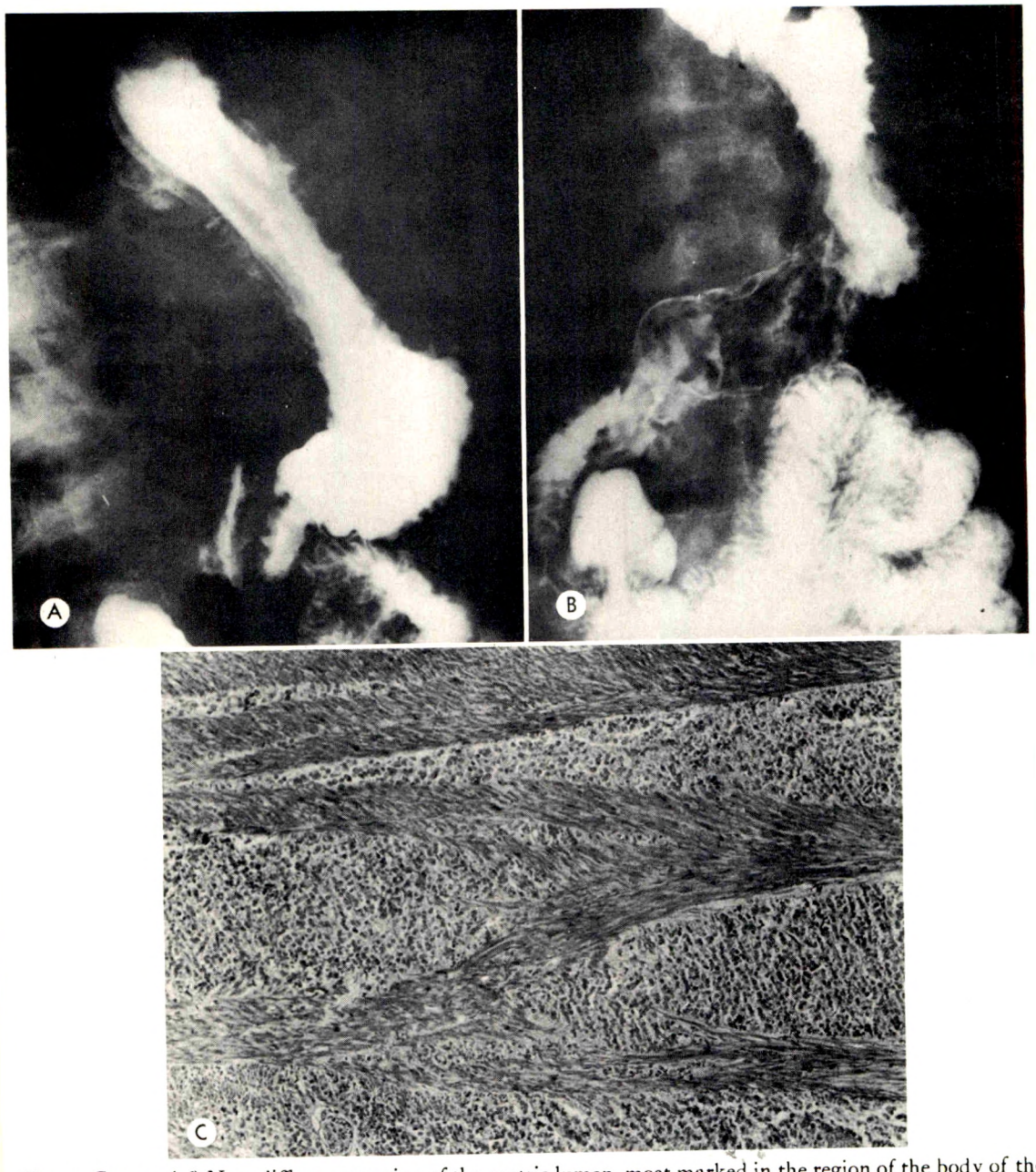

Fig. 2. Case 11. (*A*) Note diffuse narrowing of the gastric lumen, most marked in the region of the body of the stomach associated with nodularity of the lesser and greater curve aspects of its contour. Fluoroscopy showed rigidity and diminished peristaltic activity. Osteoblastic bone metastases are present in the lumbar vertebrae. (*B*) Note slightly distorted but intact mucosa. There is a large hiatus hernia and duodenal diverticulum. (*C*) Photomicrograph showing marked infiltration of the muscularis by anaplastic carcinoma cells which were identical in appearance to those of the primary breast tumor.

Case v. A 56 year old female was admitted to hospital following the acute onset of hematemesis. Three years previously she had undergone a left radical mastectomy for carcinoma of the breast and metastatic spread of this tumor was subsequently treated with hormone therapy and bilateral adrenalectomy. An upper gastrointestinal tract examination revealed a

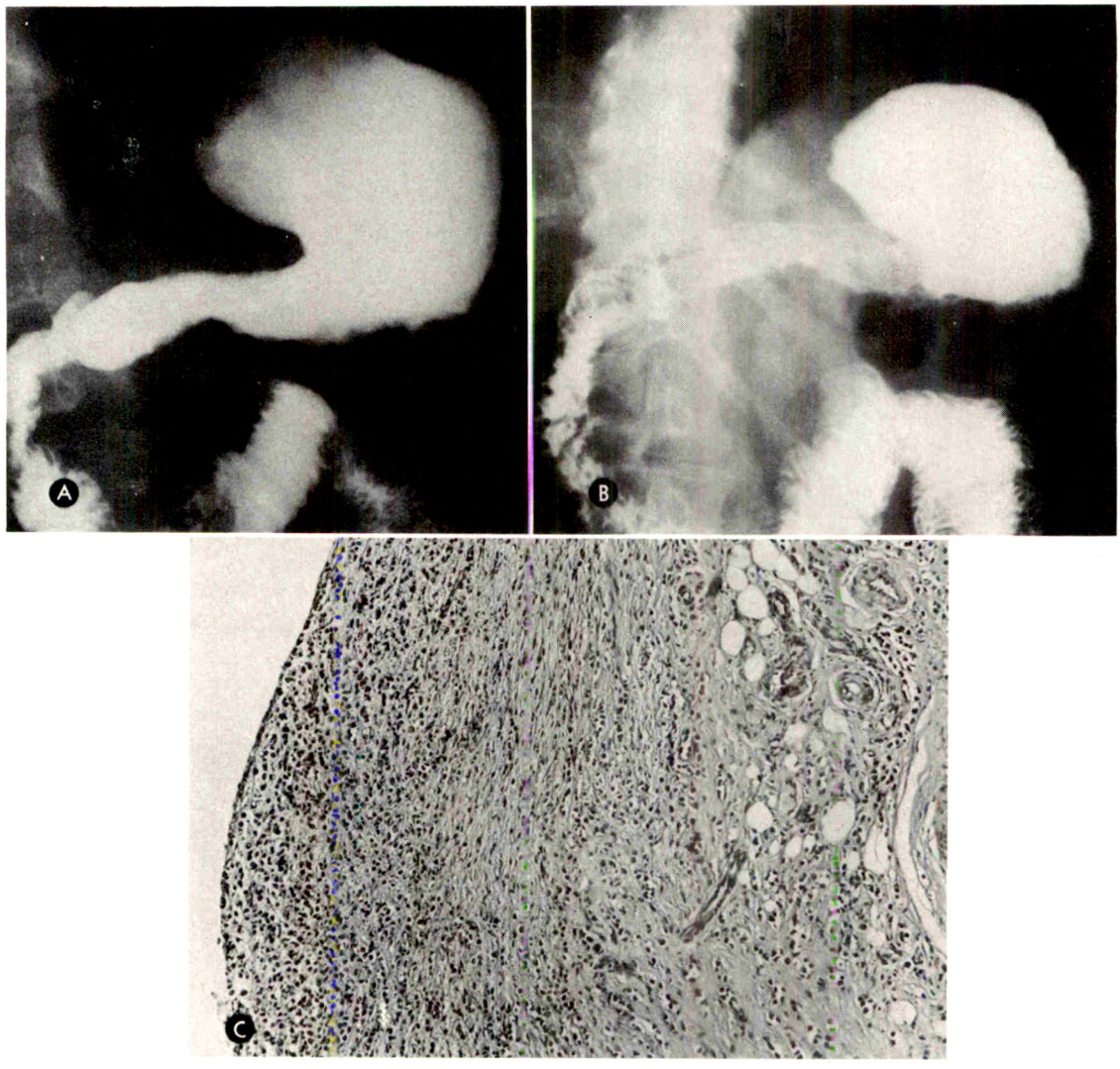

Fig. 3. Case III. (*A*) There is narrowing and rigidity of the pyloric antrum and distal body of the stomach with nodularity along the greater curve aspect. Fixation and spiculation of mucosal folds on the superior aspect of the distal duodenum suggest serosal implantation of tumor. (*B*) Note intact mucosa in the involved portion of the pyloric antrum and body of the stomach. (*C*) Photomicrograph showing diffuse tumor infiltration, most marked in the subserosal region of the gastric wall.

large discrete ulcerated filling defect in the prepyloric region of the stomach (Fig. 5, *A–C*) without evidence of gastric outlet obstruction. Widespread osteoblastic bone metastases were present in the vertebrae, pelvis, ribs and skull. A radionuclide liver scan showed several discrete intrahepatic defects consistent with liver metastases. Gastroscopic examination confirmed the presence of an ulcerated mass lesion in the distal pyloric antrum. Biopsy of this mass revealed anaplastic carcinoma similar in appearance to the original breast tumor. Following a progressive deterioration in her general condition the patient expired No autopsy was obtained

DISCUSSION

While metastatic spread of breast carcinoma most commonly involves lymph nodes, bones, lungs and liver, involvement of the gastrointestinal tract, especially the stomach and colon, is probably commoner

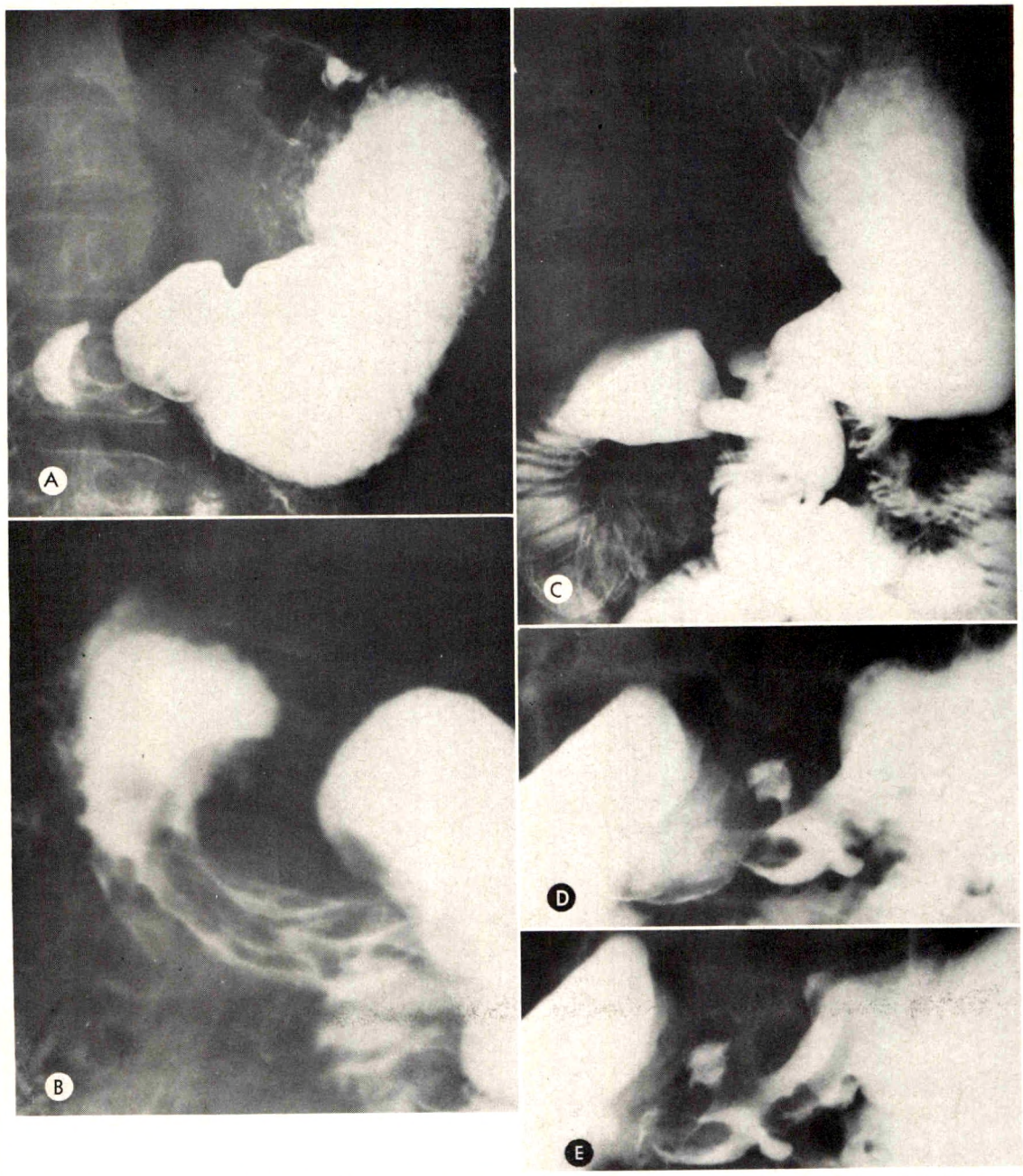

Fig. 4. Case iv. (*A*) There is a localized rigid segment of narrowing in the prepyloric region with evidence of partial gastric outlet obstruction. (*B*) Note intact mucosa in the region of the narrowed prepyloric segment. (*C*) Repeat upper gastrointestinal examination 18 months later showing at least 2 ulcer craters in region of narrowed prepyloric segment. These are well demonstrated on fluoroscopic spot roentgenograms (*D* and *E*).

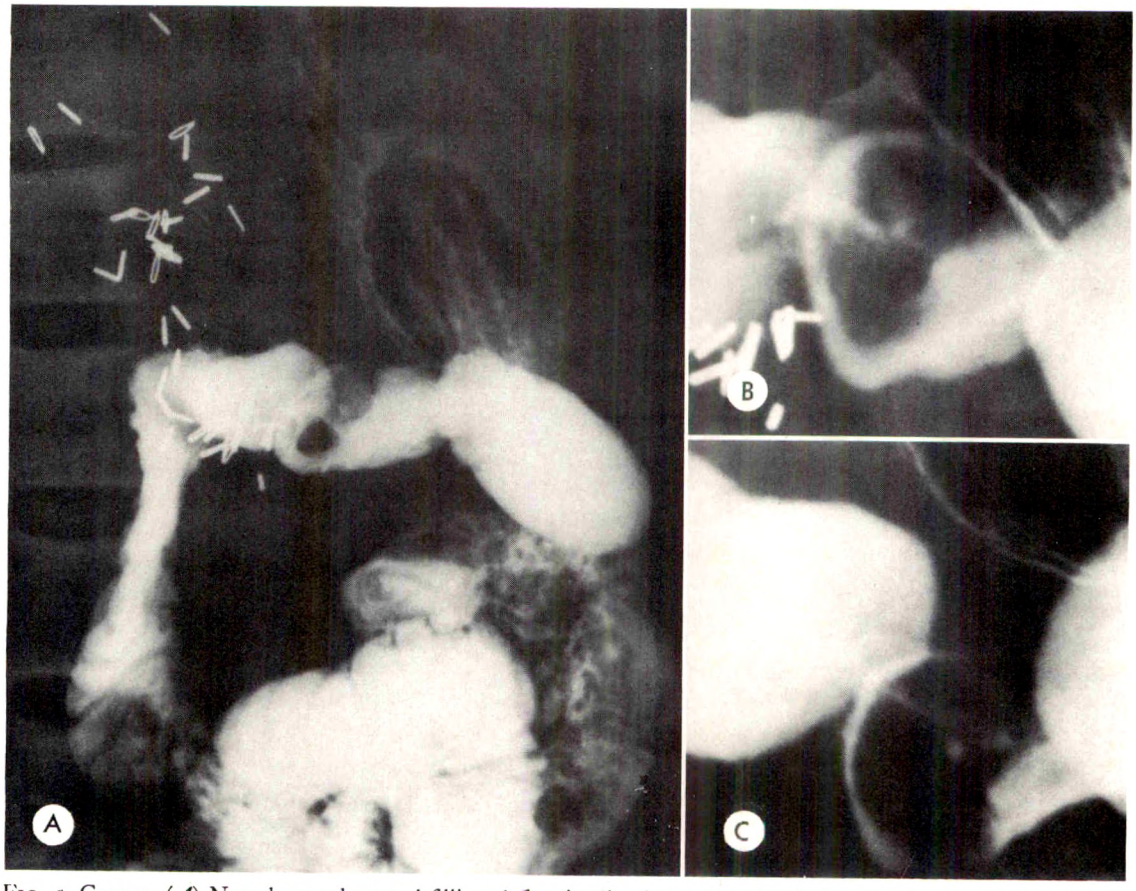

Fig. 5. Case v. (*A*) Note large ulcerated filling defect in distal portion of pyloric antrum. Osteoblastic bone metastases are present in the lumbar spine. Surgical clips are from previous bilateral adrenalectomy. (*B* and *C*) Fluoroscopic spot roentgenograms showing ulcerated mass lesion in prepyloric region.

than is generally recognized. It has been suggested by some authors that the administration of corticosteroids in patients with breast cancer is associated with an increase in the incidence of gastroduodenal metastases,[6] but this has not been substantiated by others.[5] Although it may be difficult or even impossible on the basis of clinical and roentgenologic findings to differentiate metastatic lesions from primary gastric neoplasms, this differentiation is important since it will determine the type of therapy employed, namely surgery for a new primary lesion as opposed to nonsurgical therapy (radiation, hormones and/or chemotherapy) for metastatic disease.

CLINICAL FEATURES

Abdominal symptoms may be entirely absent in patients with metastatic involvement of the stomach. This was noted in 13 of 28 patients studied at autopsy.[4] When symptoms do occur, they tend to be relatively nonspecific and generally cannot be differentiated from those due to other gastrointestinal disorders. Anorexia, nausea, vomiting and epigastric distress are the commonest complaints. These are not infrequently attributed to other gastric disorders or to the side-effects of chemotherapeutic drugs. Similar symptoms may be produced by hypercalcemia or the cachexia associated with disseminated malignancy.[5] Roentgenologic examination may not be undertaken unless symptoms are severe or persistent, or until dysphagia, gastrointestinal bleeding or signs of gastric outlet obstruction develop. Rarely, severe hemor-

rhage or obstruction may necessitate immediate surgery.[2]

PATHOLOGIC FINDINGS

Pathologic examination may reveal one of three main types of change:

i. A grossly normal stomach with microscopic foci of tumor cells in the mucosa, submucosa or muscularis. Such cases cannot obviously be diagnosed premortem.

ii. Single or multiple discrete, intramural nodular lesions with or without ulceration. According to Willis[10] most blood-borne metastatic lesions are situated initially in the submucosa forming nodules or plaques. When these enlarge and invade the mucosa, ulceration may supervene.

iii. Infiltrative lesions which may be localized or diffuse in extent and which not infrequently involve the entire stomach, resulting in gross thickening of its wall. All layers may be infiltrated, especially the submucosa and muscularis. In some cases the serosa is the site of maximum infiltration and it may be impossible to determine whether the transmural involvement resulted from a primary serosal or submucosal lesion.

The differentiation of a metastatic lesion from a primary gastric malignancy is largely based upon the microscopic findings. Histologic studies usually allow a definite diagnosis since metastatic lesions characteristically show no transition zone between the normal gastric epithelium and carcinoma cells and exhibit a histologic picture similar to that of the primary breast neoplasm.[4] According to Choi *et al.*[4] it is the poorly differentiated breast tumor which grows in rows of small anaplastic cells that most frequently gives rise to gastric metastases.

ROENTGENOLOGIC FINDINGS

Based upon the gross pathologic findings in patients with gastric metastases secondary to breast carcinoma, 2 main types of roentgenologic abnormality might be expected to occur; *i.e.*, circumscribed nodular lesions or more diffuse, infiltrative lesions. In the author's experience, as well as that of others,[3,8] the commonest type of roentgen abnormality is that produced by diffuse intramural infiltration of the stomach resulting in a linitis plastica appearance with narrowing of the lumen secondary to gross thickening of the gastric wall, rigidity and diminished or absent peristalsis in the involved area. Such infiltrative lesions may be diffuse and involve the entire stomach (Fig. 1, *A* and *B*; and 2, *A* and *B*) or may be more limited in extent (Fig. 3, *A* and *B*; and 4*A*). In either case the mucosa is often intact, especially in the earlier stages (Fig. 4*B*), although a serrated or nodular contour may be observed (Fig. 2, *A* and *B*; and 3, *A* and *B*). Occasionally, there may be roentgen changes resembling small or even large ulcer craters (Fig. 1*A*). These are apparently due to redundancy of the mucosa associated with marked submucosal infiltration and it may be difficult or even impossible to distinguish such "pseudoulcerations" from true ulcer craters on any single examination, although an unchanging appearance on serial studies over a relatively long period of time is a helpful roentgenographic feature (Fig. 1*B*). True mucosal ulceration certainly occurs in the infiltrative type of lesion but tends to develop relatively late in the course of the gastric disease (Fig. 4, *C*, *D* and *E*), and may be associated with severe gastrointestinal bleeding. Although gastric outlet obstruction is relatively rare, it may occur in association with localized infiltrative lesions in the prepyloric region (Fig. 4*A*). The linitis plastica type of metastatic breast carcinoma generally results from transmural infiltration of the stomach wall, and identical roentgenologic changes are produced irrespective of whether the lesion develops from an initial deposit of tumor cells in the submucosal or subserosal regions. Only careful pathologic examination of the distribution of tumor in the various layers of the gastric wall may give some indication as to the precise pathogenesis of the metastatic process (Fig. 1*C*; 2*C*; and 3*C*). In all 8 of our patients with the linitis

plastica type of lesion, surgery and/or autopsy examination revealed metastatic deposits elsewhere in the peritoneum so that roentgenologic examination in these patients should always include a careful search for evidence of serosal implants elsewhere in the bowel (Fig. 3*A*). Gastric metastases tend to occur late in the course of the disease and the author has not observed any cases in which metastatic spread was strictly limited to the stomach. Bone metastases were present in 6 of the 8 patients and were easily visualized in the vertebrae on roentgenograms obtained during the upper gastrointestinal series (Fig. 1; and 2).

The second type of metastatic gastric lesion secondary to breast carcinoma is that of a more circumscribed nodular lesion in which roentgenologic studies might be expected to show single or multiple discrete intraluminal filling defects with or without associated ulceration. Reports in the literature of such lesions are largely confined to autopsy studies.[4,10] Only 1 of our 9 patients exhibited this type of lesion (Fig. 5, *A–C*). The rarity of roentgenographic demonstrations of the discrete, submucosal nodular lesions, both in the literature and in our own experience, may be related to the relative lack of gastrointestinal symptoms in such patients so that roentgen studies of the stomach are rarely undertaken.

ROENTGENOLOGIC DIFFERENTIAL DIAGNOSIS

Localized and diffuse infiltrative metastatic lesions of the stomach give rise to roentgenologic changes which may be indistinguishable from a linitis plastica type primary gastric carcinoma. It may, therefore, be difficult or even impossible purely on the basis of the roentgen findings to differentiate this type of metastatic lesion from a second primary cancer. Recognition of the metastatic nature of the lesion is often largely dependent upon evidence of disseminated breast carcinoma elsewhere in the body such as in bones, lungs or liver, as well as the radiologist's knowledge of the roentgenographic pattern produced by metastatic involvement of the stomach in patients with breast cancer. In the absence of clinical or roentgenologic evidence of metastatic spread to other sites, exploratory laparotomy may be required to exclude the possibility of a potentially curable primary gastric lesion.

The roentgenologic differential diagnosis in patients with the discrete nodular form of gastric metastasis includes a fairly large number of conditions in which multiple ulcerated or non-ulcerated nodules may occur, such as adenomatous polyps, metastatic melanoma, lymphosarcoma, Kaposi's sarcoma and metastatic carcinoma from sites other than the breast. A single, circumscribed, ulcerated nodule may simulate a leiomyoma, neurofibroma, lipoma, carcinoid, pancreatic rest or even a peptic ulcer with associated edema. Because of its apparent rarity, and until more information is available with regard to the incidence of the discrete nodular form of gastric metastases from breast carcinoma, final diagnosis must depend upon histologic confirmation even in patients with disseminated disease. This will require endoscopy and biopsy in most instances, or even surgical exploration. If the possibility of simple peptic ulceration exists, especially in patients receiving steroid therapy, a repeat upper gastrointestinal examination after a period of suitable medical therapy may suffice.

SUMMARY

Apart from metastatic melanoma, involvement of the stomach by blood-borne metastatic malignancy is relatively rare.

Of the primary malignant neoplasms of epithelial origin, carcinoma of the breast is probably the commonest source of such gastric metastases.

The present paper is essentially concerned with a description of the roentgenologic manifestations of gastric metastases secondary to breast carcinoma. The clinical and pathologic features of this entity are also briefly discussed.

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A COMPARISON OF SCANS AND ANGIOGRAMS IN SELECTING PATIENTS WITH HEPATOMAS FOR HEPATIC LOBECTOMY*

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BEFORE scintillation scanning of the liver and hepatic angiography, essentially no practical methods of imaging the liver for visual inspection existed. Time and experience have provided sufficient sophistication to the application of these methods, so that they have become indispensable in the diagnosis of liver disease. We have attempted to apply them a step beyond their application for diagnosis by putting them to use in accepting or rejecting patients with hepatomas for hepatic lobectomy. This has been accomplished by assessing the liver scans and hepatic angiograms of a group of patients with hepatomas and classifying them as operable or inoperable according to certain criteria that we shall discuss.

Although several excellent articles have been published describing the angiographic findings associated with hepatomas,[2,3,12,14] and several reports have compared the roles of liver scanning and angiography in the diagnosis of hepatoma,[8,9,13] we could find no other publications evaluating liver scans and angiograms in this role of selecting patients with hepatomas for hepatic lobectomy.

We will discuss the results of the comparisons we have made and how they may be applied in the care of patients with hepatomas.

MATERIAL AND METHOD

The selective hepatic angiograms and liver scans, either gold 198 (Au^{198}) or technetium 99 m sulfacolloid (Tc^{99m}), on 35 patients, all with proven hepatomas, 12 from the United States and 23 from Japan, are included for study in this presentation. The findings on these scans and angiograms have been compared with each other and with operative and necropsy findings. One co-author (W.M.S.) evaluated the liver scans as to operability (unilobed tumors) or inoperability (bilobed tumor) without prior knowledge of surgical or necropsy findings. Tumors were considered unilobed when decreased uptake of radioactive isotope was present in one lobe of the liver only and bilobed when there was decreased uptake of radioactive isotope in both lobes of the liver.

We evaluated the angiograms as to operability or inoperability with the help of the staging system we have previously presented:[1] *i.e.*, if either neovascularity, puddling, tumor staining or abnormal avascularity was confined to the distribution of one main hepatic artery, either right or left, supplying one lobe of the liver only, the tumor was considered unilobed and therefore operable; if neovascularity etc. was obvious in the distribution of both right and left hepatic arteries or in the distribution of arteries extrinsic to the liver, the tumor was considered inoperable.

In evaluating the angiograms, we used preoperative reports whenever possible, one of us (S.L.G.) classified the angiograms

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from the 23 cases from Japan without knowledge of operative or necropsy findings. Therefore, the study is completely prospective concerning the liver scans and as prospective as possible with regard to the angiograms. The diagnoses were established histologically in every case either by needle biopsy, biopsy at operation or at necropsy.

We would like to emphasize that the diagnosis of hepatoma cannot be made from the angiogram in every case. Benign tumors of the liver such as hamartomas show changes on angiograms and scans that are identical to those shown by hepatomas. Also, many hepatomas show minimal neovascularity either because they have become necrotic or have produced much fibrous connective tissue and little neovascularity. Needle biopsies of the liver must, therefore, play an integral part in the diagnosis and acceptance or rejection of patients with hepatomas for resection. The angiogram and scan can often help serve as a guide to locate the tumor for needle biopsy.

REPORT OF CASES

Case 1. B.H., an 11 year old B.G., felt a mass in her right upper quadrant in March,

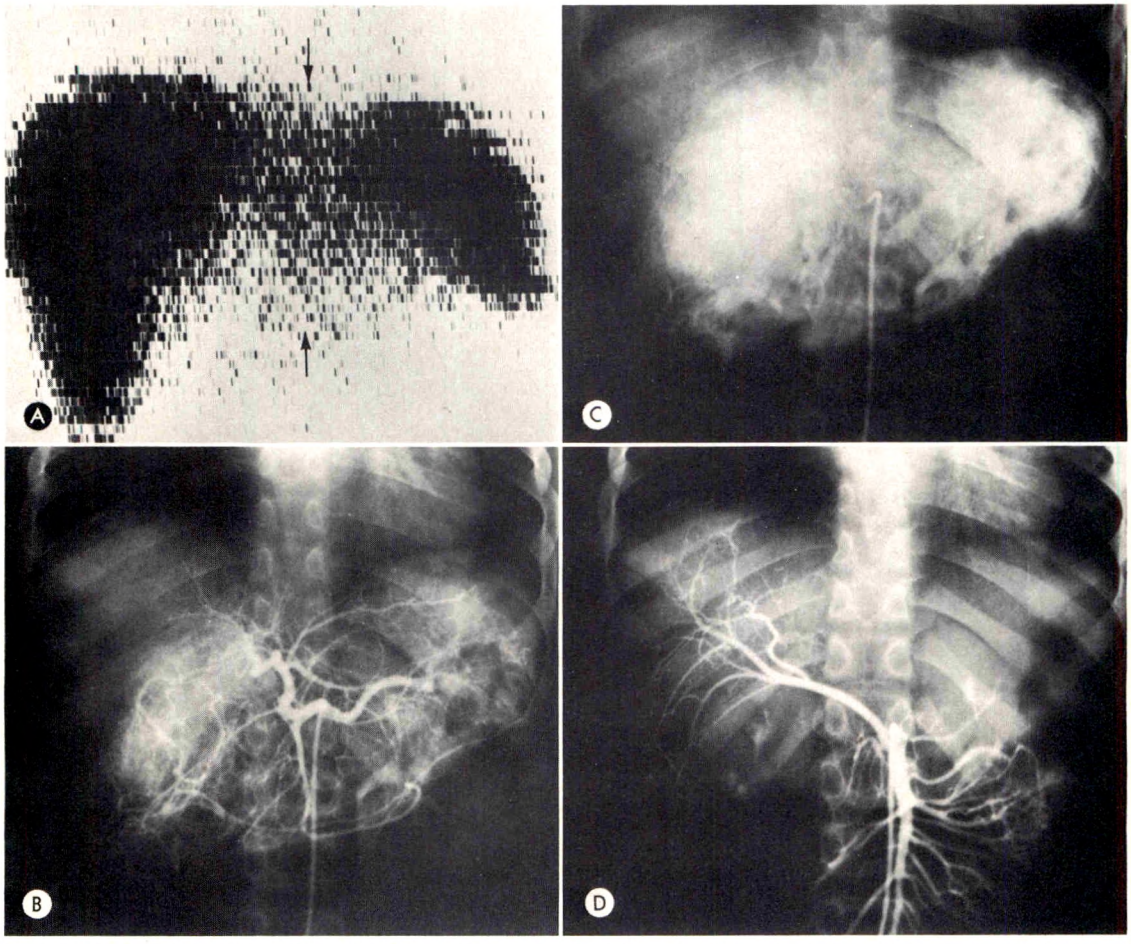

Fig. 1. Case 1. (*A*) Tc^{99m} sulfacolloid scan. Diminished uptake of radioactive isotope at junction of right and left lobes of liver suggesting a filling defect (arrows). The left lobe is superimposed on the spleen. (*B*) Celiac arteriogram. Neovascularity and staining at junction of right and left lobes. (*C*) Capillary-venous phase. Tumor stain is more evident. (*D*) Superior mesenteric arteriogram. Accessory hepatic artery originates from superior mesenteric artery and its distribution is free of tumor vascularity.

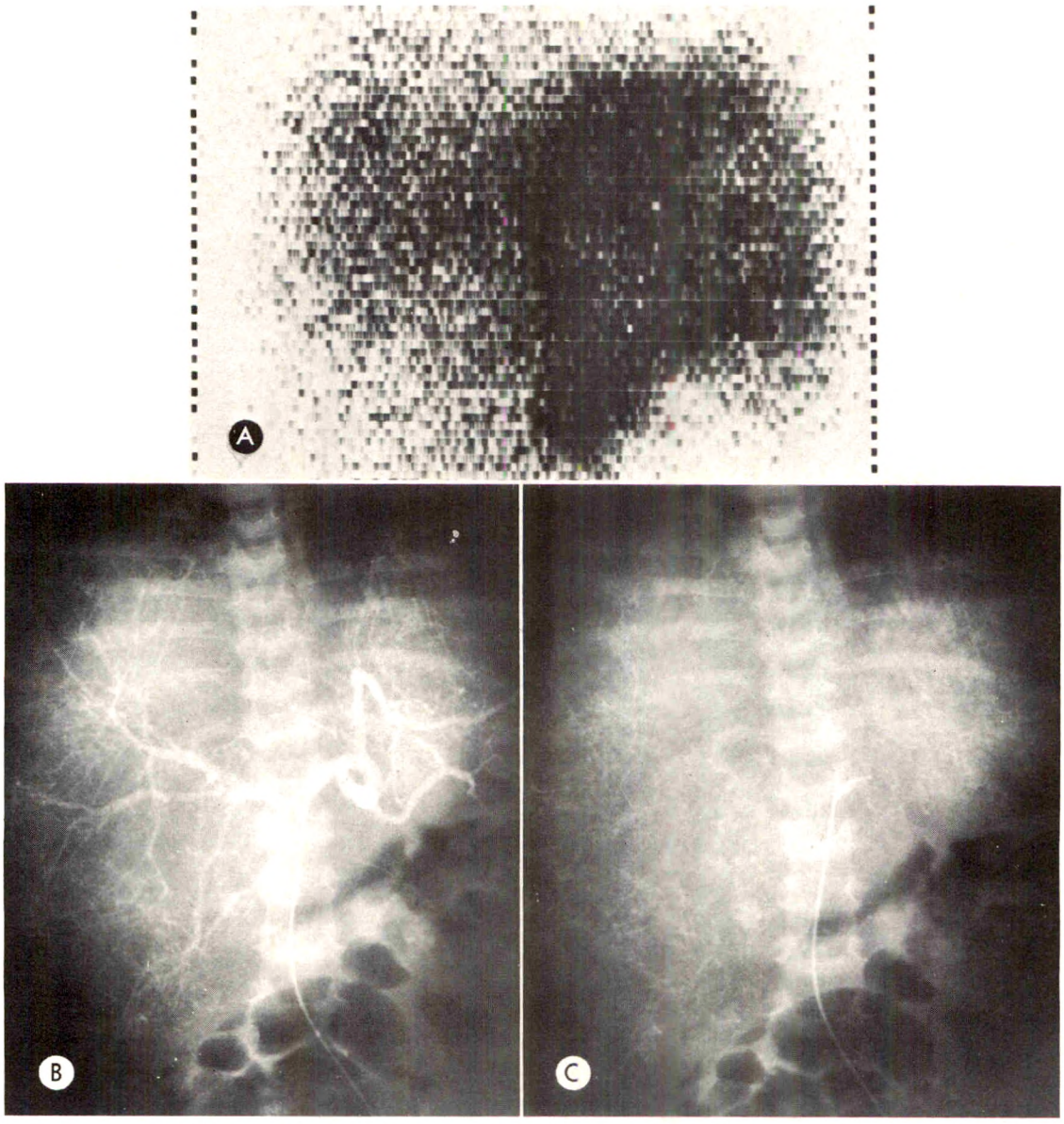

Fig. 2. Case 11. (*A*) Tc^{99m} sulfacolloid liver scan. Note decreased uptake in large and small nodules in both lobes. (*B*) Celiac arteriogram. Neovascularity is present in both lobes of the liver. (*C*) Hepatogram phase. Note puddling throughout liver as well as neovascularity.

1972. She was admitted to the hospital in June, 1972, at which time a hard mass could be felt attached to the liver. A Tc^{99m} sulfocolloid scan (Fig. 1*A*) showed a tumor located anteriorly and in or around the hilum of the liver. It was believed to have been in the hilum of the liver involving both lobes of the liver and, therefore, to have been inoperable.

The celiac angiogram showed tumor in the right lobe of the liver in the hilum (Fig. 1, *B* and *C*). There was an accessory right hepatic artery originating from the superior mesenteric artery (Fig. 1*D*). No tumor vascularity was visible in its distribution. The splenic and portal veins were normal in the venous phase and inferior vena cavagram disclosed a normal inferior vena cava.

The abdomen of the patient was explored in hopes that the tumor could be resected along with the left lobe of the liver, leaving the right

lobe that was supplied by the superior mesenteric artery intact. A mesenteric lymph node, however, contained metastatic hepatoma. A catheter was placed in the hepatic artery for perfusion of the tumor.

Comment. Neither the scan nor angiogram were actually accurate in this case. The tumor was inoperable; not because of the anatomic distribution of the tumor, but because of metastases to lymph nodes.

In 2 additional patients in the series tumor was supplied by hepatic arteries originating from both the celiac axis and superior mesenteric arteries; both tumors were inoperable.

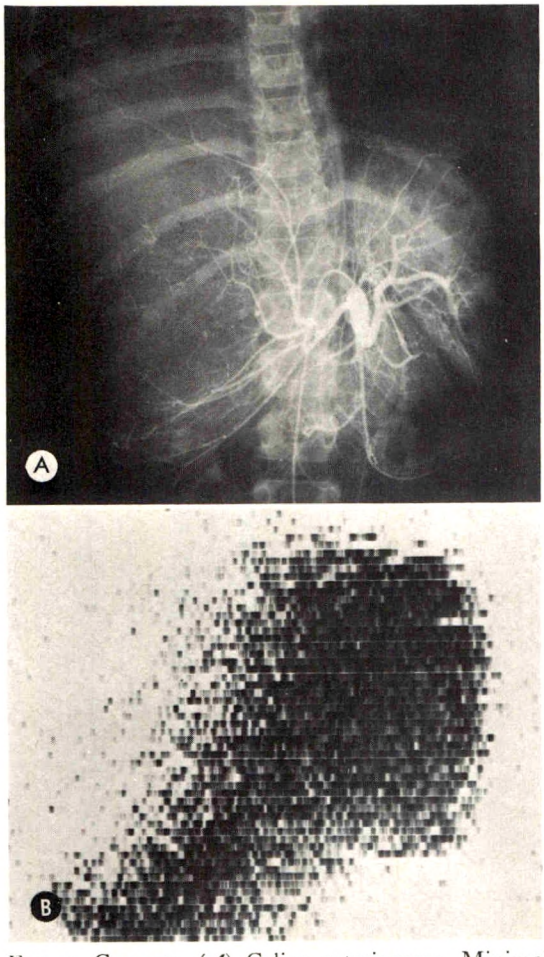

Fig. 3. Case III. (*A*) Celiac arteriogram. Minimal neovascularity in distribution of right hepatic artery in a relatively hypovascular tumor. Minimal puddling is present but no tumor staining. (*B*) Tc^{99m} sulfacolloid liver scan. There is a filling defect in right lobe, and normal uptake of radioactive isotope in left lobe.

Case II. K.S., a 3 year old J.M., was noted to have had abdominal enlargement in March, 1970. The diagnosis of hepatoma was established in June, 1970, at an outside hospital. In July, 1970, both Tc^{99m} liver scans and hepatic angiograms (Fig. 2, *A–C*) showed tumor involving both lobes of the liver. Despite these findings, however, a right hepatic lobectomy was attempted. It was unsuccessful because of excessive bleeding. Both lobes of the liver were biopsied and both contained tumor. A needless celiotomy could have been avoided with proper attention to the scan and angiogram.

Case III. Y.H., a 9 year old J.M., developed fever and nasal bleeding in May, 1970. He was not seen at a hospital until July, 1970, at which time hepatomegaly was discovered. In August, 1970, the celiac arteriogram and liver scan (Fig. 3, *A* and *B*) showed tumor confined to the right lobe of the liver. In October, 1970, a successful right hepatic lobectomy was performed and was followed by an uncomplicated postoperative course.

The patient did quite well until April, 1971, when he developed weakness and ascites followed by a regressive downhill course. He finally developed small bowel obstruction and died.

At necropsy the liver was completely free of tumor. There were, however, extensive metastases in the omentum that had apparently caused small bowel compression and obstruction. The delay of 5 months between the onset of symptoms and hepatic resection could have played a role in the development of the metastases.

Case IV. A.P., a 43 year old W.M., showed a large filling defect in the right lobe and diffuse nodular decreased uptake in the left lobe in an Au^{198} liver scan. On the celiac arteriogram, the hepatic artery was displaced inferiorly (Fig. 4*A*). There were a few tumor vessels in the lower pole of the liver, but none in the remainder of the right lobe. In the hepatogram phase, a hugh radiolucency was seen in the bulk of the right lobe with some opacification of the normal liver parenchyma around it. Biopsy proved this "radiolucency" to have been a necrotic hepatoma. We considered this patient

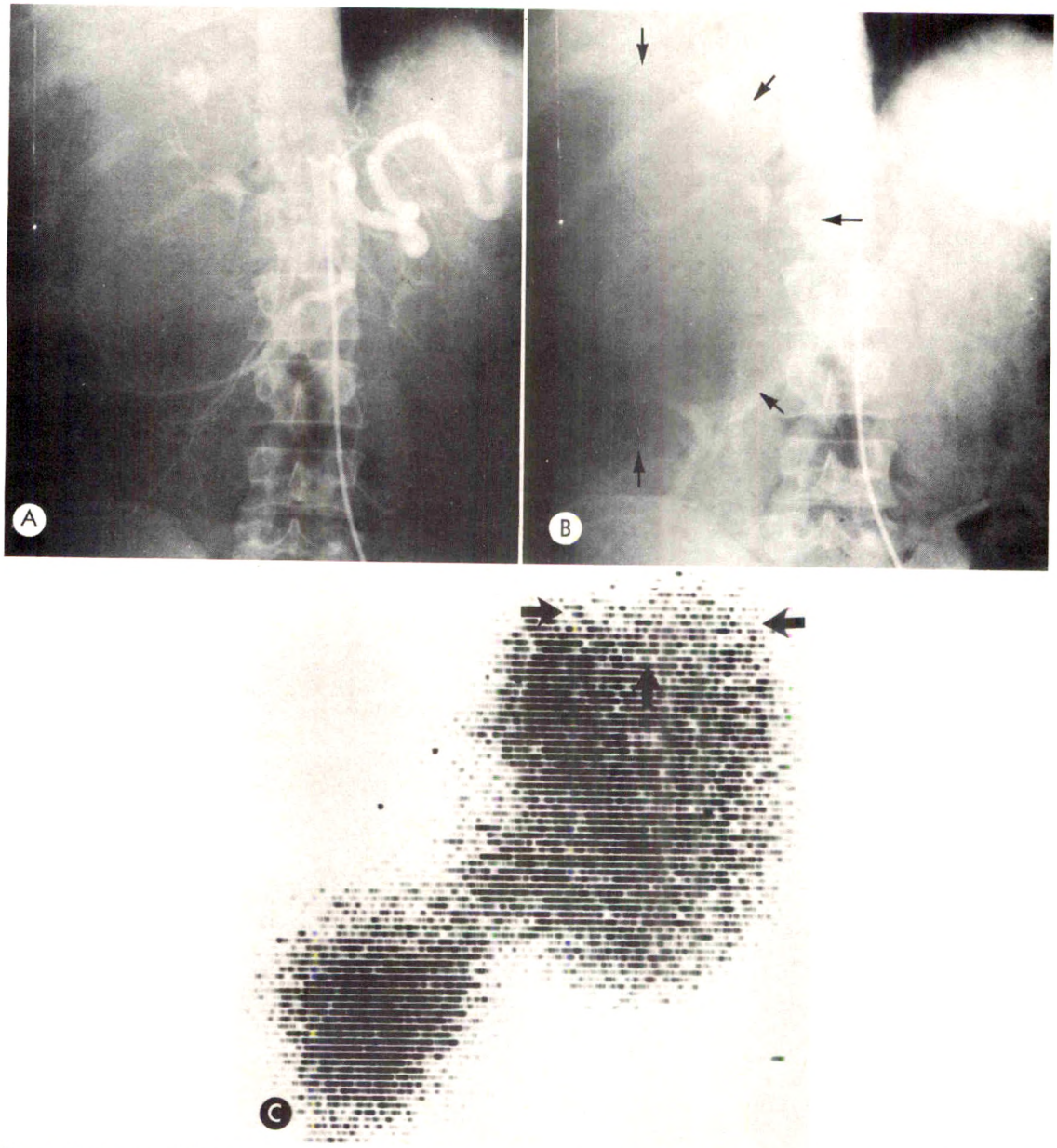

Fig. 4. Case IV. (*A*) Celiac arteriogram. Displacement and stretching of hepatic arteries with radiolucency in major part of right lobe. (*B*) Hepatogram phase. Large radiolucent defect in right lobe surrounded by opacified liver seen best by defocusing one's eyes. Also, portal vein is displaced inferiorly. No neovascularity or tumor staining is readily apparent because the tumor represented by the radiolucent defect was almost completely necrotic. (*C*) Au^{198} liver scan. There is a large filling defect in right lobe, nodular defects in left lobe and decreased uptake in nodule in upper pole of left lobe (arrows). (*A* and *B* reprinted with permission of author and *Radiology*, 1971, *101*, 549–554.)

inoperable, since the decreased nodular uptake seen on the liver scan in the upper pole of the left lobe of the liver indicated a necrotic tumor here (Fig. 4*B*) and because of the huge size of the tumor. On a follow-up liver scan 1 year later, the filling defect in the left lobe was larger, lending further support to the presence of tumor here.

The patient died shortly thereafter, but permission for autopsy was not obtained.

Case v. R.M., a 65 year old B.M., was admitted to the hospital with acute abdominal pain and hepatomegaly. Because he was believed to have been suffering from an abdominal disease constituting an acute emergency, an exploratory celiotomy was performed. A large tumor was present in the right lobe of the liver which was biopsied and reported as hepatoma. The left lobe was carefully palpated at the operation and was thought to be free from tumor. The abdomen was closed and plans were made to resect the right lobe of his liver later. Both the celiac arteriogram and Tc^{99m} sulfacolloid liver scan disclosed tumor in both lobes of the liver (Fig. 5, *A* and *B*). The operation was cancelled.

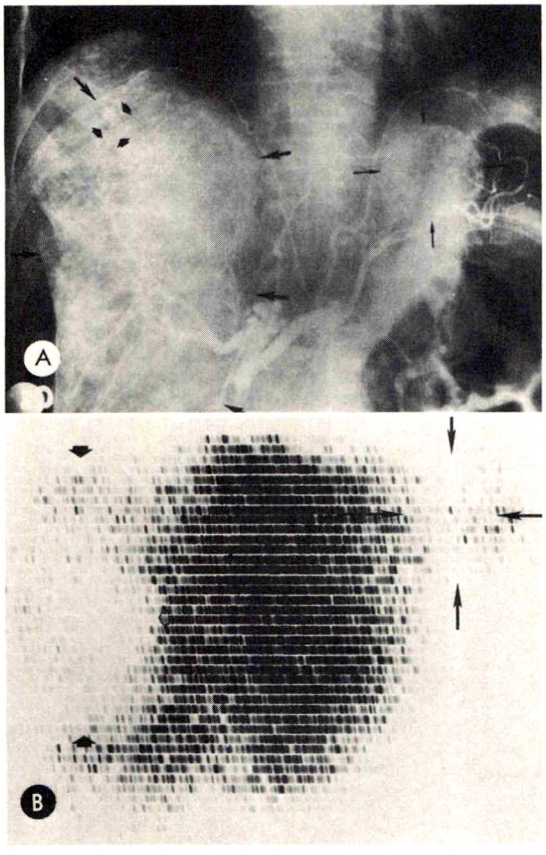

Fig. 5. Case v. (*A*) Celiac angiogram. Note neovascularity puddling and tumor staining in large nodule in right lobe (large arrows) and in smaller nodule in left lobe to the left of midline (long thin arrows). The arrowheads denote prominent puddling in the right lobe. (*B*) Tc^{99m} sulfacolloid liver scan. Note a large filling defect in right lobe (arrowheads) and a smaller filling defect in the left lobe (arrows). All isotope in the photograph is concentrated in the liver; none represents spleen.

Comment. The left lobe of the liver was normal to palpation at laparotomy, but tumor was present on the angiogram and on the liver scan. The patient was spared a needless celiotomy.

Case vi. A.G., a 60 year old B.F., was admitted to the hospital February, 1972, with a history of liver disease. A Tc^{99m} sulfacolloid liver scan showed diffuse patchy liver disease with filling defects in the right lobe (Fig. 6*A*). A liver biopsy (needle) showed hepatoma. The transfemoral hepatic arteriogram demonstrated definite tumor in the right lobe of the liver with tumor vascularity and staining in the distribution of the gastroduodenal artery (Fig. 6*B*), indicating that the tumor had spread beyond the liver and for this reason was inoperable. We, therefore, left the catheter in place in the hepatic artery for purposes of perfusing the liver with chemotherapeutic agents.

Comment. The scan showed tumor only in the right lobe of the liver, but the angiogram indicated that it had invaded the organ surrounding the liver We considered the tumor inoperable for this reason.

DISCUSSION

Of the 35 cases studied, the scan and angiogram agreed as to operability or inoperability in 27 (Table 1). Of the 27, both scan and angiogram indicated that 23 tumors were inoperable; 20 of these were inoperable at necropsy or operation. Neither operation nor necropsy was performed on the remaining 3 patients.

Only 4 tumors were operable according to both scan and angiogram (Table 1). Three of these 4 patients had tumor confined to one lobe of the liver at necropsy or operation. There were microscopic metastases to the opposite lobe of the liver at necropsy in the fourth patient. One of the 3 patients with one lobe free of disease, however, developed metastases outside the liver 6 months after operation; the liver, nevertheless, remained free of tumor. All died of complications (intraabdominal or postoperative hemorrhage and small bowel obstruction). The remaining 2 patients had

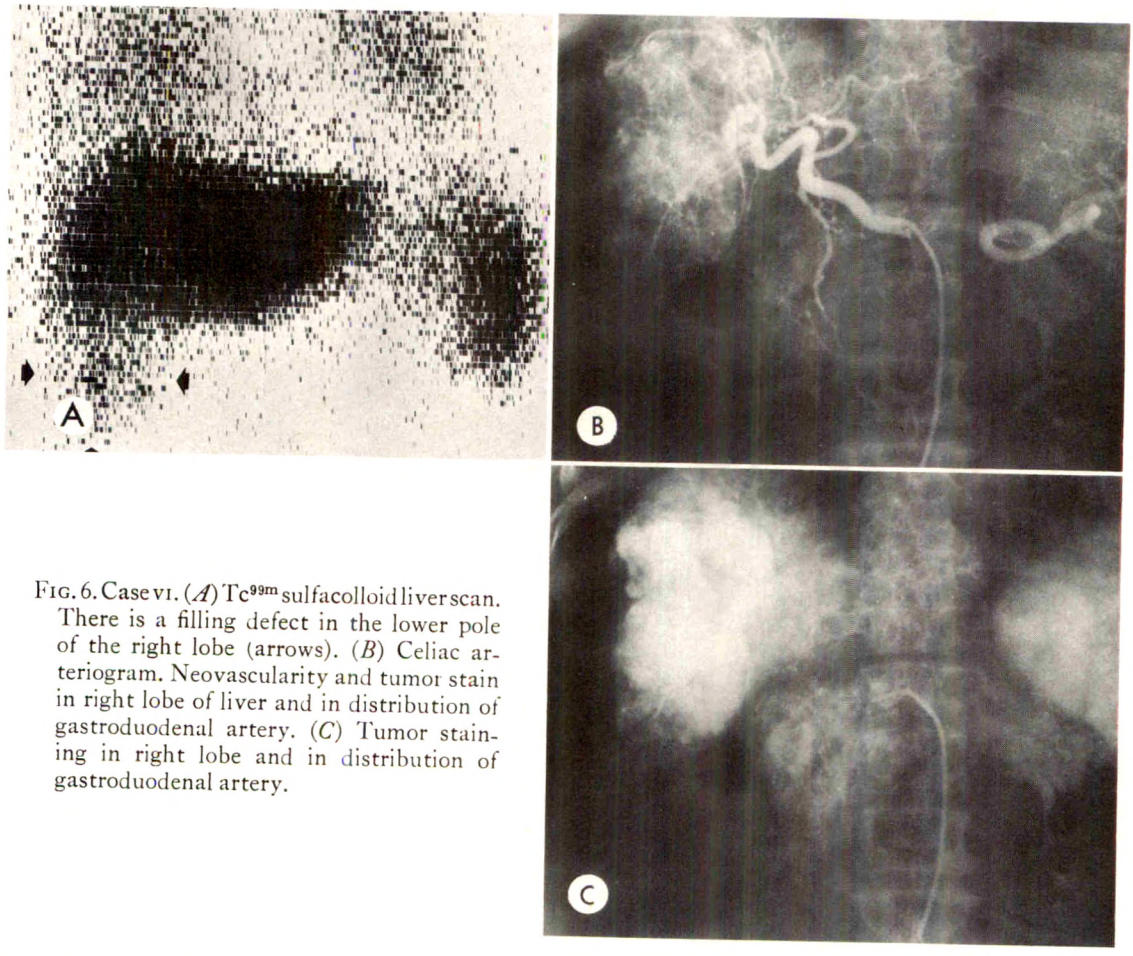

FIG. 6. Case VI. (*A*) Tc^{99m} sulfacolloid liver scan. There is a filling defect in the lower pole of the right lobe (arrows). (*B*) Celiac arteriogram. Neovascularity and tumor stain in right lobe of liver and in distribution of gastroduodenal artery. (*C*) Tumor staining in right lobe and in distribution of gastroduodenal artery.

tumor confined to one lobe of the liver without metastases.

In 8 cases the scan and angiogram did not agree as to operability or inoperability (Table II). In 5 of the 8 patients, the angiogram was correct. One reason is probably because neovascularity may be visible angiographically, indicating the presence of tumor before the tumor is large enough to become manifest on a scan. In 1 patient the scan correctly showed tumor in both lobes of the liver, whereas the angiogram showed tumor in only 1 lobe (Case III). The tumor was almost entirely necrotic and was thus more difficult to detect angiographically. The scan was correct from the clinical standpoint in 1 patient and strictly speaking neither was actually correct in 1 (Table II). Thus, according to these observations, the angiogram is usually more accurate in detecting the presence of tumor than the scan but not always. The 2 examinations are complementary and additive. Of course neither modality can detect distant metastases and "operability" and "inoperability" refer only to liver involvement and involvement of adjacent organs.

Some authors have reported discouraging

TABLE I

SCAN AND ANGIOGRAM IN AGREEMENT
(27 Cases)

A. 23 agree, inoperable	
(1) 20—inoperable by operation or autopsy	
(2) 3—no operation or autopsy	
B. 4 agree, operable	
(1) 1—had microscopic metastases to opposite lobe at autopsy	
(2) 3—operable, necropsy or operation	

Table II

SCAN AND ANGIOGRAM DISAGREED

(8 Cases)

Scans	Angiograms	Operation	Necropsy	Comments
1. Operable	Inoperable		Inoperable	Angiogram correct
2. Inoperable	Operable	Operable		Angiogram correct
3. Inoperable	Operable	Operable		Angiogram correct
4. Inoperable	Operable	Inoperable		Scan correct
5. Operable	Inoperable	None	None	Angiogram correct clinically
6. Operable	Inoperable	None	None	Angiogram correct; catheter left for perfusion
7. Inoperable	Operable	None	None	Scan correct clinically
8. Inoperable	Operable	Inoperable		Inoperable because of metastases

results concerning the survival of patients whose hepatomas were resected.[10,11] Ong and Leong[11] resected 1 lobe of the liver for cure in 101 selected patients with hepatomas and only 1 survived 5 years. This survivor died with recurrent hepatoma 6½ years after his operation. With these discouraging figures, it would seem that if one could detect extensive spread of tumor to both lobes of the liver with confidence, an operation could be omitted. Table III is an analysis of the accuracy of detecting tumor in both lobes of the liver when present (*i.e.* inoperability) by scan and angiogram. The bilobed distribution of the tumors of the 29 patients analyzed were all securely proven at necropsy or operation. In these 29 cases there were no false positives according to the angiogram. Therefore, all cases that were indicated as inoperable by angiogram were inoperable at necropsy or operation, thus providing an excellent confidence level in assessing inoperability by angiography. Since there were 2 false positives according to scans (Table III), the confidence level is lower with this modality.

Table III

ACCURACY OF ASSESSING FOR INOPERABILITY

(29 proven cases, necropsy or operation)

	No. of Cases	False Positives	False Negatives
Angiogram	29	0	3
Scan	29	2	3

It has become our policy to place a catheter in the hepatic artery following arteriography for purposes of perfusion if, as with Cases 1 and VI, reasonably good evidence indicates that a hepatoma is inoperable according to scan and/or angiogram and the diagnosis has been established histologically by needle biopsy. Of a total of 170 cases with hepatomas from our hospital, 1 survived 5 years. The hepatic artery of this patient was perfused with 5 FU. No resection was performed.

Other authors,[1,4–6] however, have reported encouraging results with survival of patients with unilobed hepatomas in whom they have resected the tumor. Accordingly, patients with unilobed tumors or perhaps tumors that involve 1 lobe and only minimally involve the edge of the opposite lobe should certainly be considered for resection of their tumor.

SUMMARY

Tc^{99m} sulfacolloid or Au^{198} liver scans and selective hepatic and superior mesenteric arteriograms from 35 patients with hepatomas were evaluated as to accuracy in predicting operability or inoperability.

The scans and angiograms agreed in 27 patients and were correct in 23 as to operability or inoperability of the tumors. They disagreed in 8 cases.

The angiograms were more accurate in predicting operability or inoperability than the scan in 6 cases; in 2 cases the scan accurately predicted inoperable tumor when the angiographic findings suggested that they were operable. The reasons for this discrepancy are discussed.

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CURRENT CONCEPTS WITH RESPECT TO CHONDROCALCINOSIS AND THE PSEUDOGOUT SYNDROME*

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CHONDROCALCINOSIS is characterized by the presence of calcium containing salts in the fibrocartilage and hyaline cartilage of one or more joints. These salts include calcium pyrophosphate dihydrate, dicalcium phosphate dihydrate, and calcium hydroxyapatite. Pseudogout is a term used to describe an acute or chronic inflammatory synovitis induced by the presence of calcium pyrophosphate dihydrate crystals in the joint, often in conjunction with roentgenographically demonstrable cartilage calcification. Numerous terms have been applied to this pyrophosphate-induced synovitis including chondrocalcinosis articularis (familiaris), crystal synovitis, chondrocalsynovitis, pyrophosphate arthropathy, pseudogout syndrome, and calcium pyrophosphate dihydrate deposition disease or CPPD deposition disease. The term pseudogout was used by McCarty and his colleagues[26] in first describing the syndrome because of the similarity of the acute attacks to that of classic acute gouty arthritis and the resemblance of the chronic arthritis to chronic tophaceous gout. Although the term may not be optimal it is widely used to identify the CPPD induced arthropathy.

INCIDENCE

The incidence of chondrocalcinosis and pseudogout is not known, since cartilage calcification is often asymptomatic. In a study of anatomy class cadavers, calcification of the menisci of the knee was found in 7 per cent.[25] This was due to CPPD crystals in 3.3 per cent of the cadavers. A roentgenographic survey of elderly persons in a home for the aged also revealed a 7 per cent incidence of knee cartilage calcification.[4]

HEREDITY

Chondrocalcinosis and the pseudogout syndrome are usually sporadic, although familial aggregates have been observed in Czechoslovakia, Chile, and the Netherlands.[37,43,44,48] The familial cases do not differ clinically or roentgenographically from the nonfamilial ones, but the onset of the disease usually occurs at an earlier age, and the arthropathy is often of greater severity and has a more rapid progression. The usual age of onset in the familial cases is in the third and fourth decades of life, whereas the occurrence in sporadic cases is usually first noted in the sixth and seventh decades or later, although the range is quite broad. In addition, the familial form is not associated with other systemic and metabolic diseases often encountered in patients with the nonfamilial form of the disease. There appears to be no sex predilection.

ASSOCIATED DISEASES

Pseudogout has been noted in association with hemochromatosis,[2,11,17] hyperparathyroidism,[7,10,16] uric acid gout,[9,14,31,38] rheumatoid arthritis,[6,14,38] and hypophosphatasia.[33] Chondrocalcinosis has also been reported in systemic lupus erythematosus,[31] ochronosis,[32] Wilson's disease,[12,13] acromegaly,[3] hemophilia,[18] and following trauma[38,46] and infection.[19] Diabetes mellitus, hypertension, atherosclerotic cardiovascular disease, and mild azotemia appear to be more

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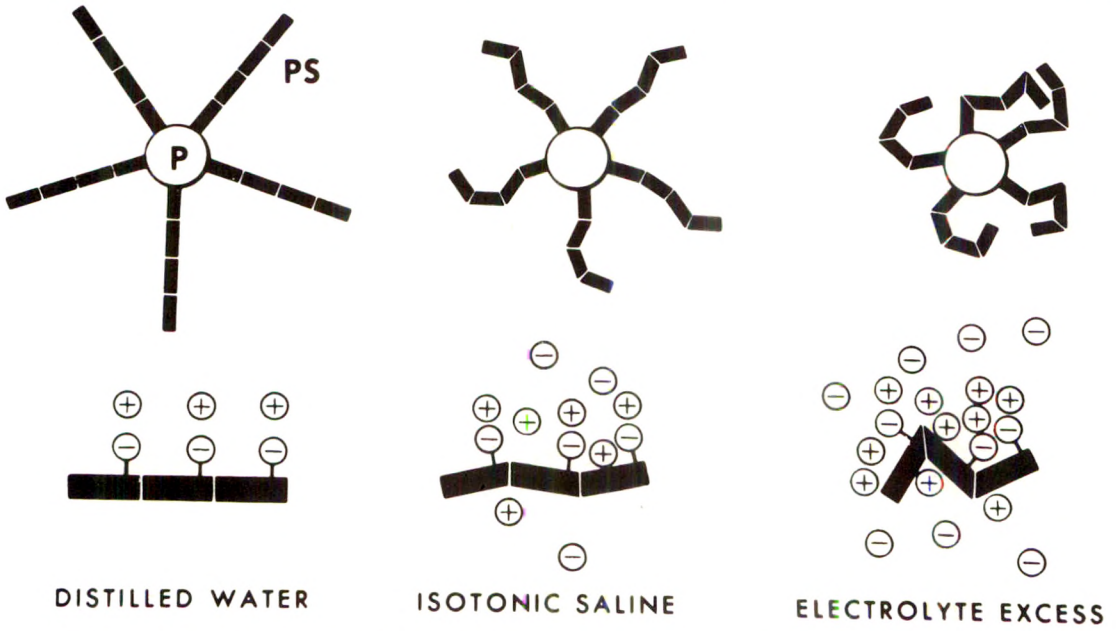

FIG. 1. Diagram demonstrating the effect of ionic charges upon the configuration of the branched mucopolysaccharide molecules of the ground substance of cartilage. Isotonic saline results in optimum extension of the branches. Excessive mutual repulsion of the fixed anionic charges occurs when the cations are removed (distilled water) resulting in increased stiffness of the cartilage. The addition of excess cations (electrolyte excess) has the opposite effect. (Courtesy of Sokoloff, L.: *The Biology of Degenerative Joint Disease*, 1969.[41])

common in patients with pseudogout than in the general population of the same age.[23] Acute attacks of pseudogout have occurred following surgery, trauma, and injection of mercurial diuretics.

PATHOGENESIS

(Fig. 1)

The mechanism by which CPPD crystals are precipitated in cartilage is unknown. McCarty[23] has suggested that the CPPD crystal represents the final common pathway for a number of metabolic disturbances. Therefore, pseudogout represents a syndrome and not a disease. He and his colleagues have postulated a defect in the metabolism of inorganic pyrophosphate (PPi), a compound produced by many biosynthetic reactions. Although the plasma PPi[1,39] and urinary PPi[34,39] are not elevated in patients with pseudogout, synovial fluid PPi is increased as much as 5 to 8-fold when compared with the synovial fluid levels found in other forms of arthritis.[1,28,39] Enzyme studies demonstrate that the levels of inorganic pyrophosphatase obtained from erythrocytes of patients with pseudogout are not significantly different from the controls.[27] This enzyme, however, is inhibited by divalent iron, calcium, and copper leading to the speculation that similar enzymes in the articular tissues might similarly be inhibited in CPPD deposition associated with hemochromatosis, hyperparathyroidism, and Wilson's disease.[27]

Divalent cations may also have another effect, namely on the biomechanics of articular cartilage. Cartilage is comprised of collagen fibrils contained in a protein-polysaccharide ground substance. When compressed, cartilage weeps fluid onto its surface much like a sponge.[29] When the pressure is removed, the fluid is resorbed. This is called self-pressurized, hydrostatic lubrication. It is accomplished by the

ground substance which has a great affinity for water and is osmotically very active due to its fixed anionic charges.[20,40,49] These electrostatic charges are also responsible for maintaining the appropriate turgor of the cartilage because they cause the extension of the branches of the mucopolysaccharide chains by mutual repulsion of the anionic charges. If the cations in the extracellular fluid are removed, increased stiffness and resistance to the mechanical expression of fluid from the cartilage develops. The removal of the cations uncovers the negative charges of the fixed anions resulting in greater than normal mutual repulsion. The addition of cations to the extracellular fluid has the opposite effect. Polyvalent cations are more effective than monovalent ones and may cause irreversible loss of elasticity of the cartilage.[41] One might speculate that the presence of abnormal divalent cations in the synovial fluid may alter the biomechanics of the cartilage, thereby accelerating damage to the cartilage and the resultant changes associated with degenerative joint disease. CPPD crystals have been demonstrated in both normal and degenerating cartilage. It has not yet been established, however, whether crystal deposition precedes the development of degenerative joint changes, or if it follows these changes. Serial roentgenographic studies by Zitnan and Sitaj[47] demonstrated progressive deposition of calcification within a joint over time as well as subsequent involvement of previously unaffected joints. Degenerative changes in these studies also progressed with time and followed the cartilage calcification. A causal relationship has not been established, however.

Injection of CPPD crystals into the joint of normal humans induces an acute inflammatory response.[24] The pathogenesis of the acute synovitis in pseudogout might be due to the rupture of preformed CPPD deposits into the synovial cavity of the joint. Phagocytosis of the crystals by polymorphonuclear leukocytes is followed by the release of a chemotactic factor from the leukocyte,[23] a phenomenon that also occurs following urate crystal phagocytosis.[35] Colchicine inhibits the release of this factor after urate crystal phagocytosis, but it is only intermittently effective in preventing the release of the chemotactic factor following CPPD crystal ingestion.[42] CPPD crystals also differ from urate crystals in that they have considerably less membranolytic effects upon erythrocytes and polymorphonuclear leukocyte phagosomes.[22,45]

CLINICAL FEATURES

Pseudogout may present as an acute, subacute, or chronic inflammatory synovitis affecting one or multiple joints. Large joints are most often involved; the knee most commonly, followed by the hips, shoulders, elbows, and wrists. Metacarpophalangeal joint involvement is common, whereas the interphalangeal joints and the great toe are less often affected. Acute attacks often have pronounced joint effusions and the presence of CPPD crystals can often be demonstrated. These crystals are rhomboid or rod shaped, are usually located within phagocytic cells, and are weakly birefringent when observed by polarized light microscopy.[36] Untreated, an acute attack will last for about 10 days. Aspiration of the effusion is often adequate for relief of symptoms. Oral administration of phenylbutazone or other anti-inflammatory agents or the intraarticular administration of corticosteroids is also effective. Occasionally there is a dramatic response to colchicine, but the effect is unpredictable. Systemic findings frequently accompany an acute attack including low-grade fever, elevated sedimentation rate, and occasionally a leukocytosis with a shift to the left which may be interpreted as indicating the presence of a septic joint.[8,23]

The majority of patients have multiple joint involvement. Repeated acute inflammatory attacks may affect the same joints, or may involve previously unaffected

Fig. 2. Frontal roentgenogram of the knee demonstrating the characteristic punctate calcification arranged in a linear pattern involving the full extent of both the menisci. There is no joint narrowing or other roentgenographic evidence of significant degenerative joint disease. Articular cartilage calcification is obscured by overlying structures and is best demonstrated on the lateral projection of the knee.

joints. Some patients develop a chronic arthritis without ever having an acute inflammatory synovitis. These patients usually have symptoms indistinguishable from degenerative osteoarthrosis consisting of low-grade arthralgias and decreased range of motion. Chondrocalcinosis, often generalized, can usually be demonstrated roentgenographically.

Roentgenographic Features

(Fig. 2–9)

Generalized chondrocalcinosis, defined as the presence of cartilage calcification in more than 2 groups of joints, is seen in the majority of patients with the pseudogout syndrome.[5,8,21,23,30] It is usually bilateral and symmetric. Both fibrocartilage and articular hyaline cartilage are involved, although the fibrocartilage is usually more extensively affected. The calcification of the fibrocartilage, most commonly noted in the menisci, triangular cartilage of the wrist, symphysis pubis and the annulus fibrosus of the spine, is characteristically a heavy punctate, sometimes diffuse opacifi-

Fig. 4. Early calcification of the triangular fibrocartilage of the wrist. The other wrist was similarly involved. Calcification was also present in the cartilages of the knees, hips, shoulders, and symphysis pubis.

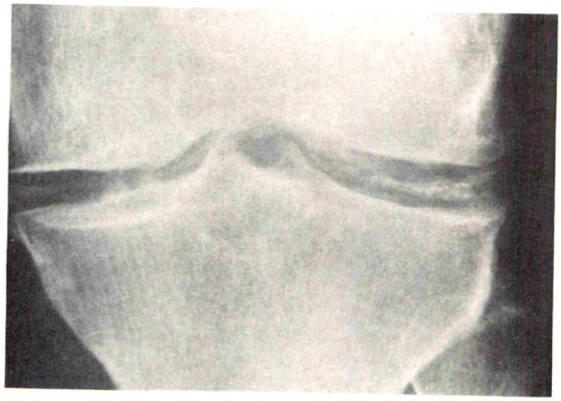

Fig. 3. Frontal roentgenogram of the knee showing dense meniscal calcification plus mild joint narrowing, irregularity of the articular surfaces, and beginning hypertrophic osteophyte formation compatible with early degenerative osteoarthrosis.

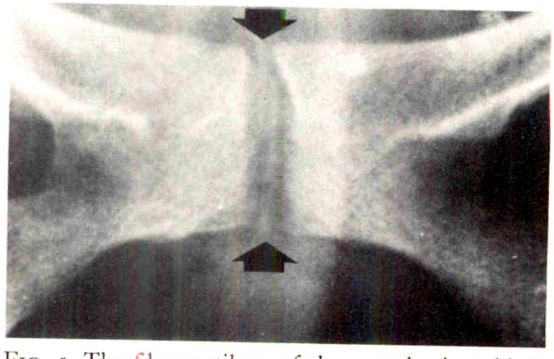

Fig. 5. The fibrocartilage of the symphysis pubis is often densely calcified in patients with generalized chondrocalcinosis and is readily identified on a routine frontal roentgenogram of the pelvis.

cation often linearly arranged. The calcification of the annulus fibrosus and the outer fibers of the intervertebral disks is often difficult to appreciate roentgenographically. Oblique views of the spine are usually more effective in demonstrating the calcification than the frontal and lateral projections. The nucleus pulposus only occasionally calcifies in this syndrome.

Articular cartilage calcification, most commonly seen in the knees, hips, shoulders, and elbows, is linear and parallel to but separated from the underlying bony cortex. Calcification within bursae, ligaments, and tendons, particularly the supraspinatus, triceps, and Achilles tendon, is also frequently present.

Joint symptoms in conjunction with the demonstration of chondrocalcinosis of the symptomatic joints often occur. However, generalized chondrocalcinosis may be noted in the absence of symptoms; joint symptoms and pyrophosphate crystals may be present in the complete absence of roentgenographically demonstrable chondrocalcinosis; or chondrocalcinosis may be present but only at asymptomatic joints, the symptomatic joints lacking demonstrable cartilage calcification or significant degenerative changes.[23,30,38] Subsequent development of cartilage calcification following joint symptoms has been noted[21] and this

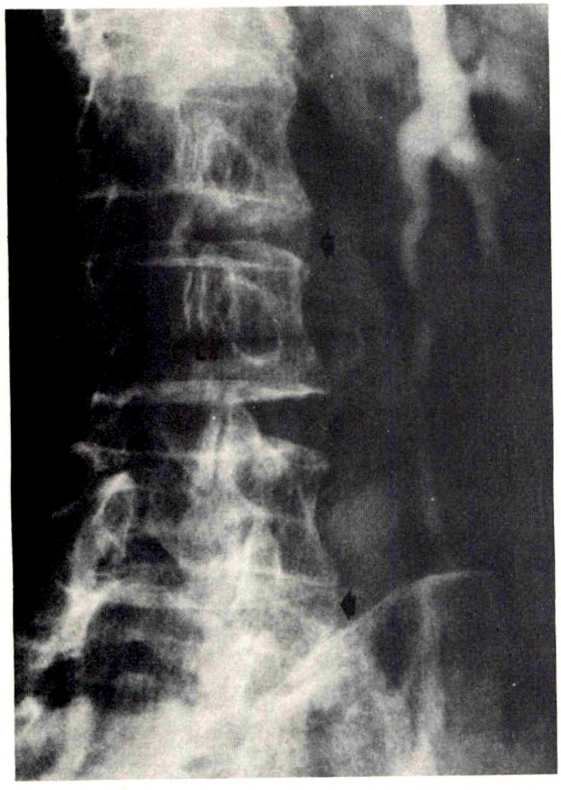

Fig. 6. Oblique roentgenogram of the lumbar spine demonstrates calcification of the annulus fibrosus at multiple levels. This calcification was not evident on the frontal roentgenogram because it was obscured by the overlying bone structures.

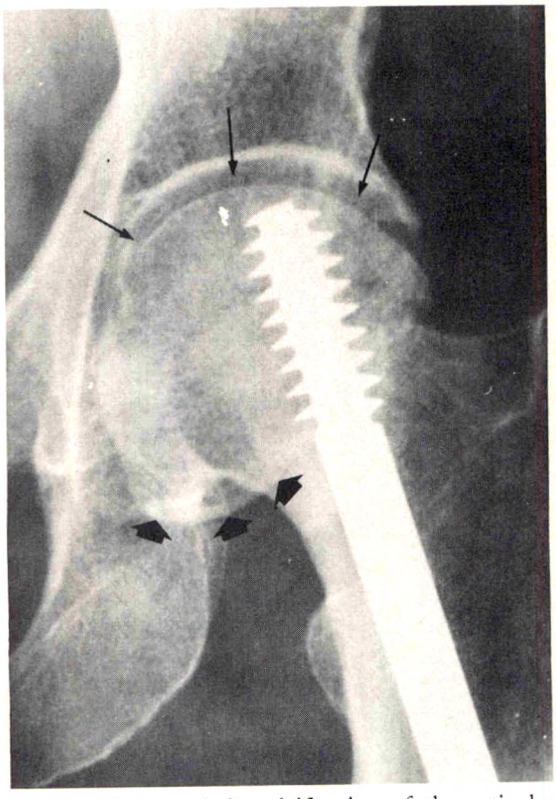

Fig. 7. Characteristic calcification of the articular hyaline cartilage (small arrows) of the hip, which is linear and parallel to but separated from the underlying bony cortex. Calcification is also present in the inferior and posterior portion of the joint capsule (large arrows). This was an incidental finding on a study obtained to evaluate the patient's hip fracture. The subsequent joint survey demonstrated generalized chondrocalcinosis and moderate degenerative joint disease. Further clinical investigation revealed unsuspected diabetes mellitus.

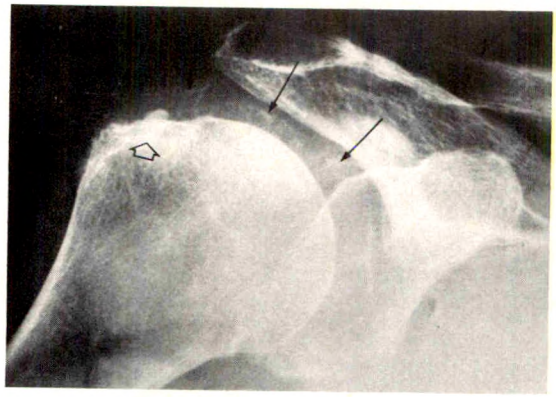

FIG. 8. Calcification in the supraspinatus tendon at the attachment of the rotator cuff (large arrow) plus calcification in the joint capsule of the shoulder (small arrows) in a patient with chronic intermittent pain in both shoulders for many years. Pseudogout syndrome was diagnosed following an acute synovitis involving the knee.

may indicate that the calcification is present but not in sufficient amounts to be demonstrated on the roentgenogram. It is not known if patients with chondrocalcinosis without joint symptoms will remain symptom-free or if they will ultimately develop arthritis and the pseudogout syndrome.

Many patients with the pseudogout syndrome have moderate to severe degenerative osteoarthrosis. This consists of joint narrowing, subchondral sclerosis, marginal osteophytes, and subchondral cysts of varying size. Paraarticular ossifications may be seen adjacent to the large joints affected with advanced degenerative changes. The distribution of the joint involvement is unusual for degenerative osteoarthrosis. The knees are most commonly affected, followed by the hips,

FIG. 9. Irregular joint narrowing, sclerosis, and subchondral cyst formation localized to the second and third metacarpophalangeal joints in a patient with hemochromatosis and generalized chondrocalcinosis. Actual bony enlargement of the metacarpal heads, not present in this case, also occurs. Involvement of the metacarpophalangeal joints appears to be more common in hemochromatosis than in the other arthropathies associated with chondrocalcinosis.[2]

shoulders, elbows, wrists, and metacarpophalangeal joints. The interphalangeal and metatarsophalangeal joints are less commonly involved. Widespread joint involvement is typical, although the most severely affected joints may not always correspond to the sites of recurrent inflammation. In the presence of advanced degenerative joint changes, chondrocalcinosis may not be demonstrated roentgenographically due to severe joint narrowing and cartilage destruction, although it is present when the joint is examined microscopically.[6]

SUMMARY

Generalized chondrocalcinosis is most commonly seen in patients with CPPD deposition disease, also known as the pseudogout syndrome. Generalized chondrocalcinosis and pseudogout in turn are commonly noted in association with hemochromatosis, which may itself be asymptomatic and clinically unsuspected.[15] Although generalized chondrocalcinosis and pseudogout have been reported in association with hyperparathyroidism, uric acid gout, and rheumatoid arthritis, a more localized form of chondrocalcinosis involving just the menisci of the knee and occasionally the triangular fibrocartilage of the wrist is usually noted in association with these diseases. Localized chondrocalcinosis has been reported in a number of entities including systemic lupus erythematosus, ochronosis, acromegaly, Wilson's disease, hemophilia, following trauma and infection, and in asymptomatic elderly persons. In addition, diabetes mellitus appears to be more common in patients with pseudogout.

Recognition of the association of chondrocalcinosis and pseudogout with these diseases is important. Clinically unsuspected disease may be identified following the diagnosis of pseudogout. Conversely, the etiology of an acute arthritis may be erroneously thought to be due to the associated disease or secondary to degenerative joint disease alone if pseudogout and the presence of the CPPD crystal-induced synovitis is not considered.

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TUMORS OF THE UPPER UROTHELIUM*

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THE epithelial lining of the urinary tract, including the renal pelvis, ureters, bladder and urethra is considered by many authors to be a continuous lining membrane (the urothelium); that of the renal pelvis and ureters forms the upper urothelium. The urothelium does not originate from one embryologic structure; the upper urothelium (renal pelvis and ureters) buds out from the mesonephric duct as it bends to join the cloaca and grows cephalad with a metanephric cap which becomes progressively larger with rapid internal differentiation (Fig. 1). The cephalad end of this bud expands to form the renal pelvis and calyces. The metanephric cap forms the kidney. The lower urothelium (of the bladder and urethra) develops from the urogenital sinus which is basically an endodermal structure with the trigone being the only mesodermal inclusion. While it is clear then that the upper urothelium develops from the embryologic nephric system and the lower urothelium from a completely independent vesicourethral unit, it seems that the similar function of both parts has welded them into a largely homogenous system. Be it as it may, one fact is indisputable: the components of the upper urothelium—calyces, renal pelvis and ureters—have a common origin.

Anatomically the system starts with a varying number of minor calyces (4–12) which unite to form 2–3 major calyces which join the renal pelvis. The calyces are intrarenal, the renal pelvis partly extrarenal and the ureter curves down from the pelviureteric junction to the uretero-vesical opening (Fig. 2) making a smooth S curve along its travel of about 30 cm. The whole system is enclosed in a slab of tissue less than 30 cm. long and 10 cm. wide, which lies along the vertebral column from the level of the first lumbar vertebra to the level of the second or third sacral vertebra. This fact is important when radiation therapy is considered.

Studies concerning the lymphatics of the

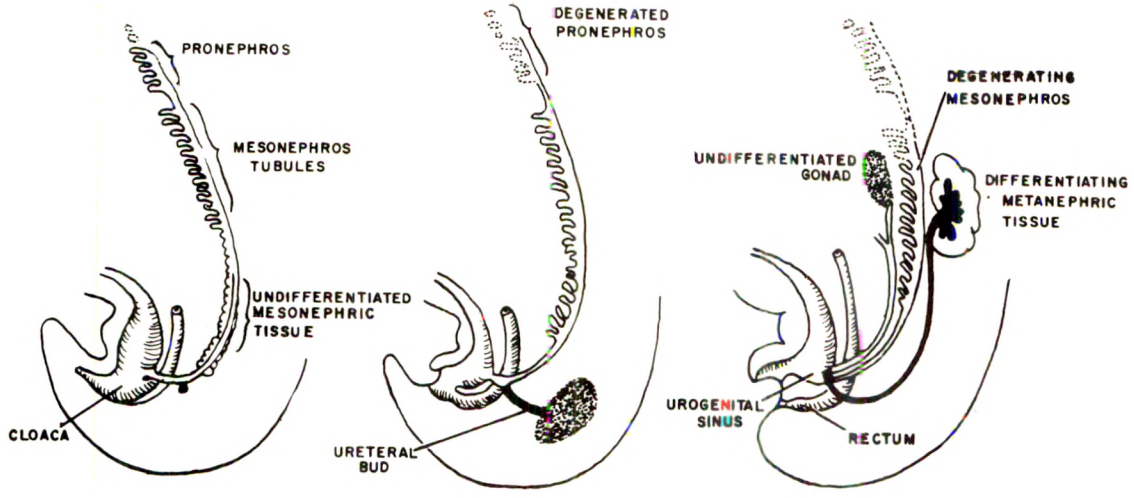

FIG. 1. Representation of the development of the upper urothelium (calyces, pelvis, ureter). (Redrawn from General Urology, Donald R. Smith, Large Medical Publications, Palo Alto, California.)

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upper urothelium are meager. Those of the upper portion of the ureter, pelvis and calyces drain into the paraortic or lumbar lymph nodes. The lymphatics of the mid-ureter drain into the hypogastric and common iliac lymph nodes. The lower ureteral lymphatics drain into the vesical and hypogastric nodes. It is impossible to decide about the thorny question of whether there is any crossing of the lymphatic drainage from one side to the other and to what extent, but it would be safe to conclude that while the paraortic lymph nodes may be considered as one group of lymph nodes, the iliac lymph nodes may be safely treated as unilateral units. Lymphatic flow seems to be influenced by increased fluid pressure in the renal pelvis or ureter which results in reflux into lymphatics and veins. An obstruction caused by tumor, for example, may predispose to reflux into lymphatics which may encourage lymph node involvement.

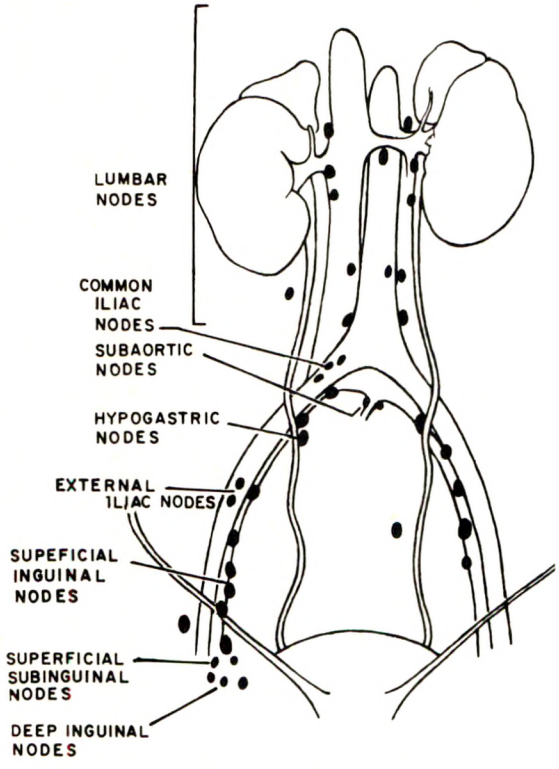

Fig. 2. Anatomy of the urothelium with lymphatic drainage.

All the 3 components of the upper urothelium, calyces, renal pelvis and ureter are of similar histologic structure. The pelvis and ureter are composed of 3 coats: outer fibrous, middle muscular, and inner mucosal. Except for the presence of renal papillae (in the calyces) which are covered with a single layer of cuboidal epithelium, the mucosal lining is identical with that of the bladder and mainly transitional. There are no real glandular elements in the mucosa. The musculature is composed of 3 layers: an inner and outer longitudinal layer with a more marked interposed circular layer. The structure of the whole unit is eminently suitable to fulfill its main function which is the transport of urine necessitating continuous mobility of the muscle layer with a frequency varying between 1 and 5 contractions per minute. Despite the continuous activity of the ureter the thickness of the muscle layer in normal conditions is only a few millimeters, a most important point when studying the local spread of tumors. The epithelial lining, which gives rise to almost all tumors of the upper urothelium, is much more permeable to water than to other solutes (except for urea) which results in a higher concentration of these solutes—a point of special relevance if any of these solutes happens to be carcinogenic such as naphtylamine or benzidine compounds.

This understanding of the evolution of the upper urothelium, its anatomy, and physiology is necessary for the appreciation of the spread and natural history of its tumors which are for the most part tran sitional cell carcinomas or rarely squamous cell carcinomas. Since they were first described by Rayer in 1841 in his publication, "Traités des Maladies du Rein" (quoted by Mazeman[15]), these tumors have proved to be rare and recent published works are rather scanty. The largest series published was that by the French urologist Etienne Mazeman,[15] who undertook an exhaustive review of 1,118 cases assembled from the experience of many urologic centers. Grabstald *et al.*[9] reported on a total of 79 pa-

tients, seen at the Memorial Hospital of New York in over a third of a century (1932–1969), averaging about 2 cases a year. Only 1 of 4,000 cases seen in the Urology Clinic in Queen Mary Hospital of Hong Kong[21] is reported to be carcinoma of the renal pelvis. Williams and Mitchell[31,32] reported a total of 43 cases of renal pelvis carcinoma seen in 20 years (1951–1970) in addition to 54 ureteral carcinomas seen in the same period. Grace and his colleagues[10] reported 37 cases of renal pelvic carcinoma seen in Ohio State University Hospital in 15 years, and Newman and colleagues[19] reported on 59 cases of pelvic and ureteral carcinomas seen in 12 years.

If reports on carcinomas of the upper urothelium are meager, up-to-date radiotherapy experience is almost nonexistent. Of the 1,118 cases collected by Mazeman[15] only 120 were treated by radiotherapy with a variety of doses and for such a maze of objectives that a meaningful analysis is impossible. Mazeman[15] concluded that radiotherapy has several possibilities and should be tried on a more systematic basis. In the 43 cases of carcinoma of the renal pelvis reported by Williams and Mitchell[31] only 1 case was treated by radiotherapy and none in a series of 54 cases of ureteral carcinoma. The same was noticed in the series reported by Petkovic,[22] Grabstald *et al.*,[9] Newman *et al.*,[19] Dufour,[7] and Rometti *et al.*[25] This complete lack of modern radiotherapeutic approach is mainly due to an inherited belief that these tumors are rather radioresistant.[18,28,29] Cases included in most of these series were treated without the benefit of modern radiotherapeutic equipment and methods of treatment planning and dosimetry. Two other important facts should be contemplated by the concerned oncologist. Firstly, the present results of treatment by the most extensive procedure recommended (nephroureterectomy) is unsatisfactory; the 5 year survival is around 35 per cent for the moderately differentiated,[31] and drops to 15 per cent for the poorly differentiated carcinoma. The 10 year figures are dismal, averaging 10 per cent. Secondly, transitional cell carcinomas of the upper urothelium are histologically, and in most other aspects, almost identical with bladder carcinoma.[6] The latter is radiosensitive and the place of radiation in its treatment is widely reported. It would be logical then to explore the role of radiotherapy in the management of tumors of the upper urothelium and its effect on the natural history of the disease.

MATERIAL AND METHOD

Forty-two cases of tumors of the upper urothelium are reported in this study. All but 1 originated in the renal pelvis; the remaining tumor originated in the calyceopelvic junction. Of the 42 lesions, 28 were transitional carcinomas and 14 were squamous cell carcinomas. This relatively high incidence of squamous cell carcinomas (33 per cent) is probably a sampling error rather than a true figure, which is reported to be about 10 per cent.

There is an opinion in the surgical literature that squamous cell carcinomas are more radiosensitive than transitional cell carcinomas, which would explain the preponderance in our series composed of cases seen in a radiotherapy department.

SEX AND AGE INCIDENCE

Women form about one-third of the patients seen (17 of 42) with a somewhat increased percentage (Table 1) in cases of transitional cell carcinomas (42 per cent), compared to squamous cell carcinomas (35 per cent). Figure 3 shows the distribution of the cases among different age

TABLE I

SEX INCIDENCE

	Transitional Cell Carcinomas	Squamous Cell Carcinomas	Total
Male	16	9	25
Female	12	5	17
Total	28	14	42

groups. The tumor is extremely rare before the fourth decade of life. Our youngest patient was a 38 year old male. While transitional cell carcinomas occur more often during the 5th and 6th decades of life, squamous cell carcinomas seem to occur with the highest frequency in the seventh decade of life. The wide claim that squamous cell carcinomas are linked to the presence of a local irritant for lengthy periods of time may explain the late age incidence. Indeed 2 of those patients had frank long-standing lithiasis.

The right and left kidneys are affected almost equally in both transitional cell (15 and 13, respectively) and squamous cell carcinomas.

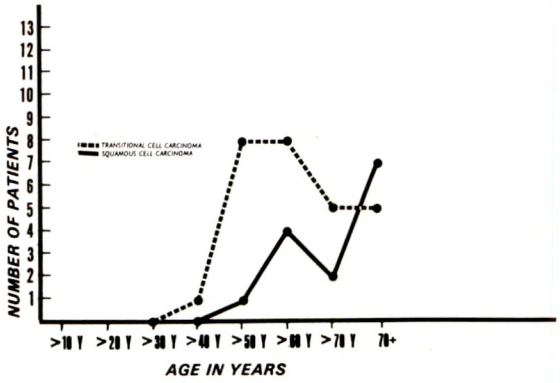

Fig. 3. Distribution of cases among different age groups.

SPREAD OF PELVIC TUMORS

Spread of pelvic tumors may be to urothelium, renal bed (Table II) lymphatics or distant organs (Table III). Involvement of the ipsilateral ureter as well as the ureterovesical junction is well documented,[14] and had led to the wide adoption of nephroureterectomy as the operation of choice.[9] This mode of spread was described on 21 occasions in the 28 transitional cell carcinomas in our series: 11 in the ureter; 8 in the bladder; and 2 in the urethra. On the other hand, it occurred only on 4 occasions in the 14 squamous cell carcinomas reported; 2 in the ureter and 2 in the bladder. This difference between the spread of transitional cell carcinomas and squamous cell

Table II

LOCAL SPREAD OF TUMORS OF RENAL PELVIS

	Spread to Urothelium				Spread to Kidney	
	Total No. of Cases	Ureter	Bladder	Urethra	Renal Bed	Parenchyma
Transitional cell carcinoma	28	11	8	2	10	3
Squamous cell carcinoma	14	2	2	—	8	2
Total	42	13	10	2	18	5

Table III

SPREAD TO DISTANT ORGANS

	Total No. of Cases	Spread to Lymphatics	Spread to Distant Organs		
			Bones	Lungs	Splanchnic Organs
Transitional cell carcinomas	28	4	4	2	2
Squamous cell carcinomas	14	4	2	2	1
Total	42	8	6	4	3

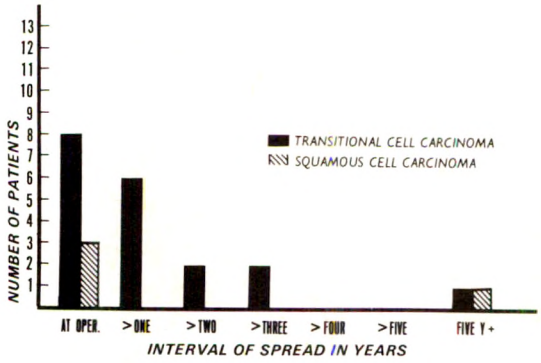

FIG. 4. Spread of disease to urothelium.

carcinomas (75 and 28 per cent, respectively) is significant ($p=0.01$), and, together with the fact that the latter spreads to the renal bed far more frequently than the transitional cell carcinomas (57 and 35 per cent) signifies an important difference in the natural history of both tumors. The spread of these tumors to urothelium seems to be in a systematic fashion. The ureter was involved before the bladder in all the cases studied and the latter before the urethra. Bladder involvement started at the ureteric opening and adjoining areas with eventual wider extension.

About half the incidences of extension to urothelium were discovered at presentation (Fig. 4), and a further third occurred in the first year. However, later recurrences are not unknown; in 2 of our cases this happened in the 6th and 7th year of follow-up. The great majority of squamous cell carcinomas seem to demonstrate this route of spread at presentation, the 1 tumor that was discovered during the seventh year of follow-up (in a patient treated for a squamous cell carcinoma of the pelvis) was a transitional cell carcinoma in the bladder. The same observation applies to the renal bed involvement (Fig. 5); most of the incidents are demonstrated at presentation or in the first year, especially in cases of squamous cell carcinomas. It appears that the natural history of the latter is much shorter than that of transitional cell carcinomas and that recurrences in squamous cell carcinomas occur almost always during the first year of follow-up.

SPREAD TO LYMPHATICS

Spread to lymphatics occurred in 4 cases (of 14) of squamous cell carcinoma (28 per cent), as compared to 14 per cent in the transitional cell carcinomas (4 of 28). Two-thirds of incidences of lymphatic involvement are demonstrated at presentation (Fig. 6) and the remainder in the following 2 years of follow-up.

SPREAD TO KIDNEY PARENCHYMA

Involvement of the kidney parenchyma occurred in 3 of the 28 transitional cell carcinoma cases (10 per cent) and in 2 of the 14 squamous cell carcinomas.

DISCUSSION

While the limited number of cases restricts the significance of these observations, it seems that transitional cell carci-

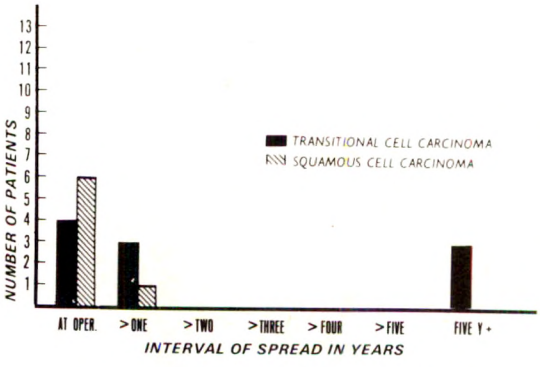

FIG. 5. Spread of disease to renal bed.

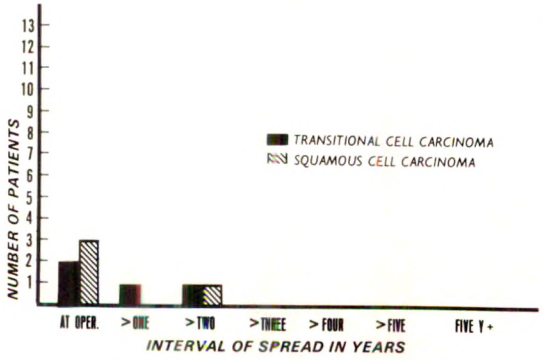

FIG. 6. Spread of disease to lymphatics.

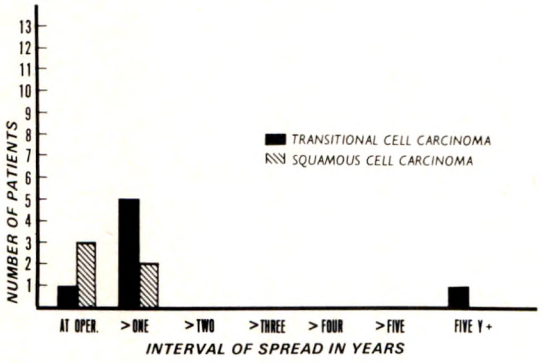

Fig. 7. Spread of disease to distant organs.

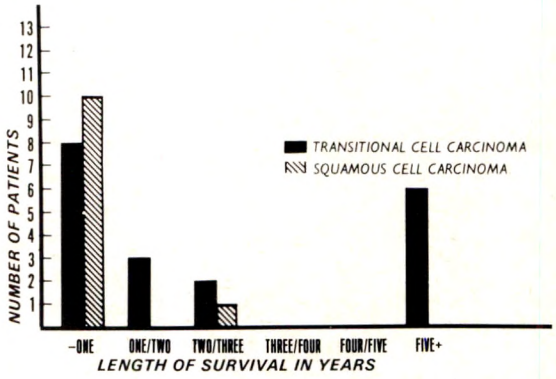

Fig. 8. Pattern of death of patients from disease.

nomas spread mainly through the urothelium in an apparently systematic fashion (*i.e.*, ureter, uretero-vesical, bladder, urethra, other ureter, and pelvis), while squamous cell carcinomas spread locally involving the renal pelvic bed, kidney parenchyma, and lymphatics. Spread to distant organs occurs with almost equal frequency in both histologic types (Table III): in 8 occasions in transitional cell carcinomas (4 in bones, 2 in lungs, and 2 in splanchnic organs); and on 5 occasions in squamous cell carcinomas. The majority of these metastases occur in the first year of follow-up (Fig. 7) but about a third of the cases have already metastasized by the time of presentation. A picture of a far metastasis, *e.g.* a pathologic fracture, may indeed be the presenting symptom. The fact that the natural histories of transitional cell and squamous cell carcinomas are distinctive from each other is re-emphasized when one studies the pattern of death of patients suffering from this disease (Fig. 8). The great majority of patients (10 of 11) suffering from squamous cell carcinomas die in the first year, while only 40 per cent (8 of 19) of those suffering from transitional cell carcinoma do the same. The difference is of some statistical significance ($p=0.06$). Moreover, 30 per cent of those who died with transitional cell carcinoma do so after the lapse of 5 years from the date of treatment to the primary—an indication of the importance of a long period of follow-up and of the limited value of 5 year results.

RESULTS

The 5 and 10 year results of treatment are seen in Tables IV and V, where 43 per cent (10 of 23) of those suffering from transitional cell carcinomas survived for

Table IV

FIVE YEAR RESULTS OF TREATMENT

	Total No. of Cases	No. of Cases Lost	Five Year Results				
			No. of Cases at Risk	Alive and Well	Alive with Disease	Dead with Disease	Dead without Disease
Transitional cell carcinomas	25	2	23*	6	4	13	—
Squamous cell carcinomas	14	1	13	2	—	11	—
Total	39†	3	36	8	4	24	—

* One patient died with another malignancy—mixed mesodermal tumors of uterus.
† Three patients are recent.

TABLE V

TEN YEAR RESULTS OF TREATMENT

	Ten Year Results				
	No. of Cases at Risk	Alive and Well	Alive with Disease	Dead with Disease	Dead without Disease
Transitional cell carcinomas	14*	1†	—	13‡	—
Squamous cell carcinomas	10	2	—	8	—
Total	24	3§	—	21	—

* One patient died of mixed mesodermal tumor.
† In 1 patient disease recurred after 15 years in left loin, proven histologically.
‡ One patient died postoperatively with a presumed local recurrence.
§ Recurrence of lesion in 1 patient occurred after 13 years. Patient still alive with disease.

over 5 years. However, only 26 per cent were free of disease and the remainder had some evidence of recurrent disease. Out of the 14 patients who were followed for 10 years, only 1 survived free of disease. The 5 and 10 year results of patients suffering from squamous cell carcinomas are 15 and 20 per cent, respectively (2 of 13; and 2 of 10). It is worth noting that Gahagan and Reid,[8] in a review of 196 cases collected from literature in 1949, found no 5 year cures. The same was noted in a review of 275 cases reported by Dees.[6]

Among the factors which are claimed to influence the prognosis of transitional cell carcinomas are the grade of the tumor, the extent of involvement of the viscus wall,[30] and the kidney permeation.[9] However, little is known about the relation between different types of tumor recurrences and its subsequent behavior, especially those in the urothelium, renal bed, lymphatics and distant organs.

URETER DISEASE

As most of our patients were treated with nephro-ureterectomy, we have studied the natural history of those patients who suffered from extension of disease to the ureter at operation as well as those who had subsequent recurrence. Figure 9 shows the mode of spread of disease in 10 patients: 8 presenting with transitional cell; and 2 with squamous cell carcinomas. The great majority of patients suffered from lymph node metastasis[6] followed by local recurrences in the renal bed.[5] Only 3 patients suffered from extension of disease to bladder, and in 2 the disease extended to urethra. How-

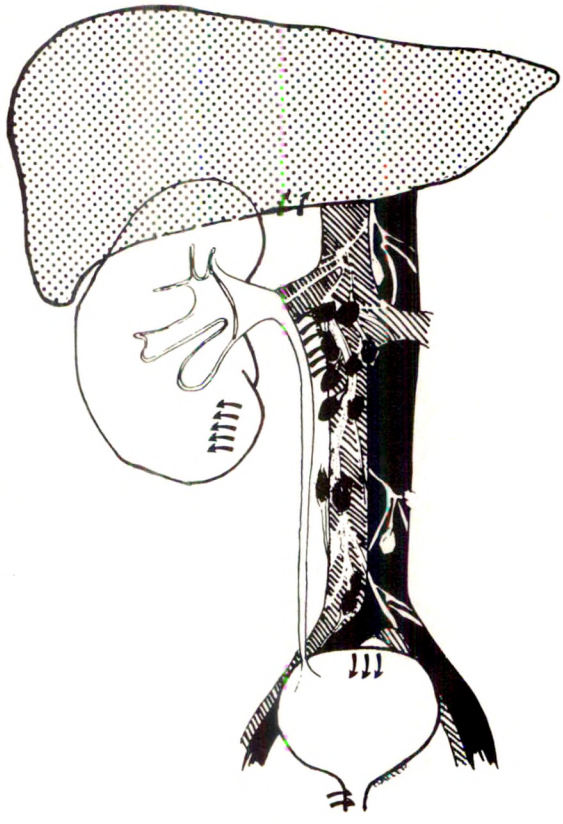

FIG. 9. Representation (by number of arrows) of spread of disease in ureter, to renal bed, lymphatics, bladder, and urethra.

ever, bladder and urethral disease seems to be both easily controlled by surgery or radiotherapy and accompanied with rather long survivals. Both patients who suffered from recurrent disease limited to the urothelium lived for over 8 years. This is in great contrast to the 16 months that was the average survival period of the other 8 patients.

BLADDER DISEASE

Of 8 patients who suffered from bladder disease, 2 were diagnosed at time of nephroureterectomy and the remainder were discovered later—after an average period of 49 months (Fig. 10). Subsequent successful management salvaged 2 patients. The average survival of patients after discovery of bladder disease is 52 months. The cause of demise of all those who succumbed seems to be their bladder disease.

RECURRENCE IN RENAL BED

Recurrence of disease in the renal bed was reported in 8 cases. The average period of delay before incidence of such recurrence is rather long averaging 5 years and 7 months (6 cases), but it seems that once this occurred eventual fatal outcome occurred in a matter of months. Only 1 patient (of 8) was salvaged after a successful excision of the recurrent mass.

LYMPHATIC SPREAD

Lymphatic involvement was reported in 9 cases: 7 discovered at operation; and 2 demonstrated later. All but 2 died with lymph node metastatic disease after a rather short period averaging 9 months. One patient is recent and still under treatment. The remaining patient died with bladder disease after 3 years. Paraaortic lymph nodes are most commonly affected as they are the first nodal station (Fig. 2), but left supraclavicular and even axillary lymph nodes may be involved as occurred in 1 case. Metastatic lymph nodes can be controlled by radiotherapy, as happened in the latter case with survival of over 1 year after radiation treatment.

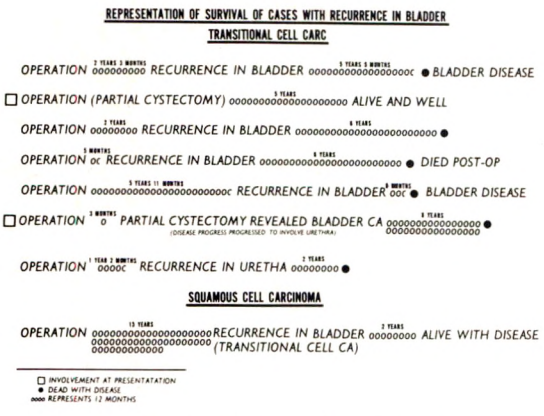

Fig. 10. Representation of survival of cases with bladder recurrence.

METASTATIC DISEASE

It is often difficult to decide about the length of survival after the incidence of metastatic disease due to the inaccuracies in determining the incidence date of the latter. The average length of survival of patients who expired with metastasis was 19 months (from date of first presentation for treatment) for those suffering from transitional cell carcinomas (8 patients) and 6 months for squamous cell carcinomas (4 patients). It appears that the development of distant metastases in squamous cell carcinomas often signifies early fatal outcome.

THE ROLE OF RADIATION THERAPY

Fourteen patients were treated with irradiation to various stages of the disease (Fig. 11). Treatment to the primary tumor by irradiation alone is extremely rare, occurring when patients are either poor surgical risks or refuse surgery, and then only for palliative reasons. While histologic diagnosis is usually unattainable except at autopsy (as happened in 1 case) cytologic confirmation is always there. One case was a transitional cell and the other a squamous cell carcinoma. The dose used in the first case was 1,600 rads but the dose in the second case was 5,500 rads to the kidney as well as an adjoining mass of paraaortic lymph nodes. Both patients died of their disease after a few months (9 and 7 months,

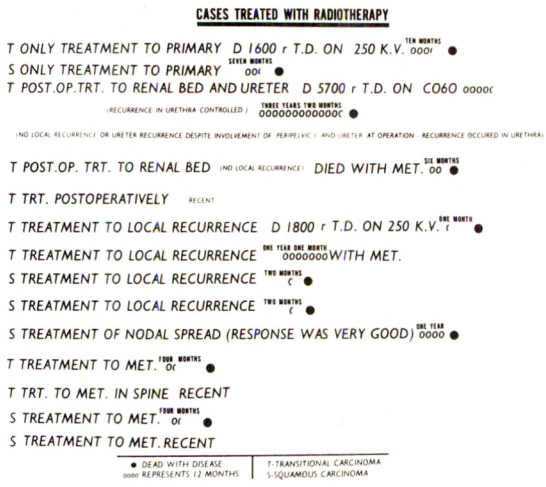

Fig. 11. Representation of survival of patients treated with radiotherapy.

respectively). Radiation therapy to the primary tumor is usually successful in stopping bleeding, but its value in palliating pain due to mass pressure or in achieving growth restraint is rather dubious. The fact that these tumors seem to be poorly vascularized, as invariably demonstrated by angiograms (Fig. 12, *A* and *B*) would explain the poor response of such a tumor mass to irradiation. On the other hand, renal cell carcinoma which is much more vascularized has been demonstrated to be more responsive to radiotherapy even though some time must elapse before changes are demonstrated.[24] The long natural history of transitional cell carcinoma makes palliation worthwhile.

Three patients received postoperative treatment to the uretero-renal bed. All 3 displayed evidence of involvement of peripelvic tissues at operation. The dose aimed at is 5,000–5,500 rads in about 5 weeks. All 3 continued to be free from local recurrence, although 1 developed a recurrence in the urethra, which was treated by a radical dose of radiotherapy with complete disappearance of the disease (histologically proven) and no recurrence during a follow-up period of over 3 years. However, the patient succumbed to metastatic disease. The second patient (Case IV) displayed similar findings and results. The third patient is a recent one.

While the response of the primary tumor

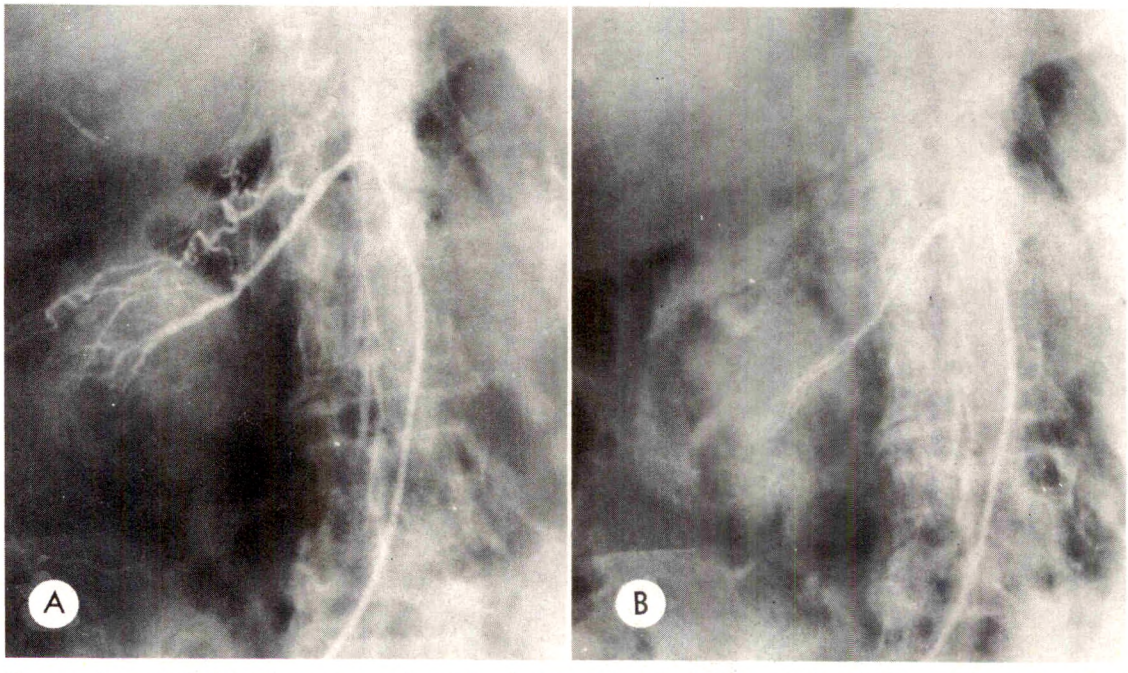

Fig. 12. (*A* and *B*) Selective renal angiograms of a case of renal pelvic transitional cell carcinoma showing 2 renal arteries, hypovascularization of the region of the tumor and a faint tumor vessel blush (*B*).

to radiation is rather limited, the control of postoperative subclinical (or microscopical) disease by adequate radiotherapy should be attainable. Transitional cell carcinoma of the bladder, which is akin to that of the renal pelvis, can be sterilized by irradiation, demonstrating the radiosensitivity of these lesions. The technique employed is rather simple, a field 25–30 cm. long, modulated according to the anatomy of the urothelium (Fig. 13, *A* and *B*) including the major part of the bladder on the side of the tumor is used. The volume should include the paraaortic lymph nodes, but the other kidney should be completely protected. It seems from the study of the natural history of the disease that postoperative radiotherapy is specially indicated when the tumor has involved the pelvic bed, kidney tissues, lymphatics or when the tumor is of high-grade malignancy (Grades III and IV).

Radiotherapy to local recurrence has met with little success, since the disease is rather extensive by the time of presentation. Aortography did not contribute much to the early diagnosis of these recurrences in contrast to recurrences after renal cell carcinomas which are usually more vascular. Of the 4 cases treated for recurrence only 1 was controlled and the patient (Case VII) lived for over a year to succumb to metastases. The average survival period in the remaining 3 patients was less than 2 months.

Lymph node metastases seem to respond well to adequate radiation doses. Case X displayed lymph node metastases to supraclavicular and cervical regions, which responded extremely well to radiotherapy with subsequent survival of over 1 year.

Treatment to metastases, especially those in bone (Cases XI, XII, XIII, and XIV) by radiation is an effective method of pain control.

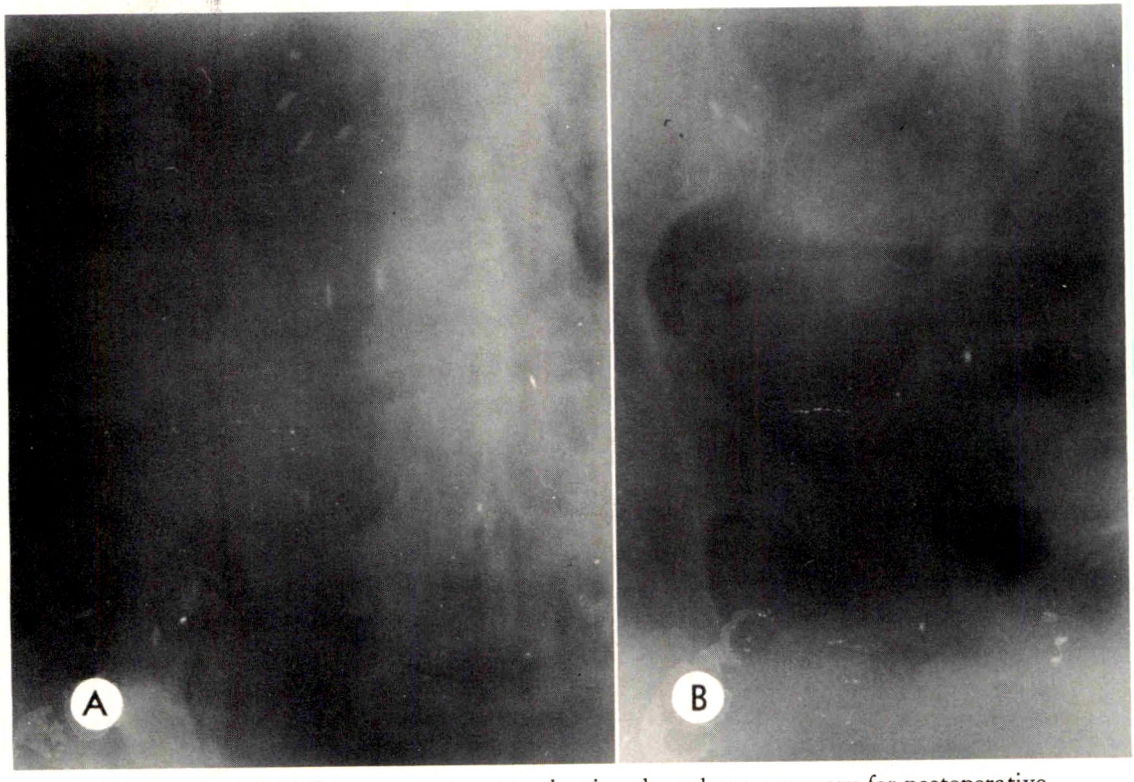

Fig. 13. (*A* and *B*) Spot roentgenograms showing the volume necessary for postoperative treatment of an upper urothelial tumor.

SUMMARY

Forty-two cases of malignant tumors of renal pelvis were reviewed: 28 were transitional cell carcinomas; and 14 were squamous cell carcinomas.

The natural history and spread of the disease is discussed in detail. Transitional cell carcinomas spread primarily to the ureter (40 per cent), followed closely by the renal bed (33 per cent) and bladder (30 per cent). Squamous cell carcinomas spread primarily through the renal bed (60 per cent), followed by the draining lymph nodes (28 per cent). The spread to other regions (bones, splanchnic organs, chest . . . etc.), occurred with relatively less frequency, but more in squamous than transitional cell carcinomas. Transitional cell carcinomas seem to have a longer natural history than squamous cell carcinomas. Recurrences in bladder and the remainder of the urothelium seem to be controlled for relatively long periods of time, while those in lymph nodes and renal bed seem to be rapidly fatal.

The results of treatment and factors influencing them are discussed. Patients suffering from transitional cell carcinomas faired better than those with squamous cell carcinomas at the 5 year mark (25 and 15 per cent, respectively), but the 10 year results are poor in both.

The role of radiotherapy in the treatment of these tumors and the influencing factors are also discussed in detail. The response of these tumors to radiotherapy seems to be akin to that of the lower urothelium (bladder), provided adequate dosage is delivered to the relevant volume at the proper moment in time.

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RENAL VENOGRAPHY IN THE EVALUATION OF POORLY VASCULARIZED NEOPLASMS OF THE KIDNEY*

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MOST primary malignant renal neoplasms are easily diagnosed by selective magnification renal arteriography. In some cases, however, poorly vascularized infiltrating tumors may have subtle nondiagnostic findings at arteriography, while selective renal venography may reveal the characteristic malignant nature of these elusive tumors. This report describes the application of selective renal venography in evaluating such tumors.

MATERIAL AND METHOD

Six patients are included in this report, all with hematuria, in whom intravenous pyelography revealed a mass lesion. Two patients had nephrotomography which suggested that the mass was solid. The other patients had selective renal arteriography following the initial intravenous pyelography. Our method of selective renal venography represents a modification by one of us (J.R.) of a method described in 1965 by Olin and Reuter.[8] Venography was performed immediately following the selective renal arteriography, utilizing the same selective arterial catheter. A total of 8–10 micrograms of epinephrine was infused over 20 seconds into the renal artery, followed immediately by an injection of 30 ml. of meglumine diatrizoate (Renografin 76) at a rate of 12–15 ml./second into a second catheter placed in the ipsilateral renal vein. The filming sequence was 2 films/second for 5 seconds; magnification technique was utilized. We have used a straight polyethylene catheter (yellow Cook material with I.D. of 1.50 mm. and O.D. of 2.26 mm.) with multiple side holes, introduced into the renal vein over a Cook tip deflector wire. Alternatively, a catheter with a gentle curve may be used, eliminating the need for a tip deflector, although the caudally directed catheter tip may cause predominant contrast material flow into the veins draining the lower pole of the kidney.

RESULTS

In all 6 patients, the selective renal arteriogram revealed minor arterial irregularities that were nonspecific in nature, and the definitive diagnosis of malignancy could not be made. Furthermore, 3 of the 6 patients had epinephrine renal arteriography which was also inconclusive. The epinephrine venogram, however, demonstrated changes of encasement and amputation indicating malignancy in all 6 cases, despite the vague arteriographic findings. Three patients had the final pathologic diagnosis of transitional cell carcinoma, while each of 2 patients had an avascular hypernephroma, and 1 had a metastatic squamous cell carcinoma from a lung primary.

DISCUSSION

The simplest and most direct method of demonstrating the morphology of the renal venous bed is by selective catheterization of the renal vein, with retrograde injection of contrast material against the flow of blood. The peripheral intrarenal veins will rarely be filled, however, in the presence of normal renal blood flow. Attempts to slow

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renal blood flow mechanically with balloon catheters in the aorta, inferior vena cava and renal vein are generally cumbersome.[11] An alternate method, that of pharmacologic slowing, was introduced in 1965 by Olin and Reuter,[8] consisting of an injection of epinephrine into the renal artery through a selective catheter, followed by rapid injection of contrast material into the ipsilateral renal vein. Subsequent reports have emphasized the value of this method in renal parenchymal disease,[5] and in the nephrotic syndrome.[4]

Renal venography has seldom been considered in the work-up of renal masses, since the diagnostic accuracy of arteriography is quite high. Angiographers, however, have long been aware of the difficulty in detecting poorly vascularized renal malignancies, notably transitional cell carcinoma and poorly vascularized renal cell carcinomas. Fortunately, only about 2 per cent of all renal cell carcinomas are hypovascular, since the arteriographic findings in these cases can be misinterpreted as representing a benign renal cyst.[7] Similarly, the arteriographic changes in transitional cell carcinoma can be very subtle even with an extensively infiltrating tumor, and consist mainly of increased size of the pelviureteric artery, a mottled nephrogram, fine neovascularity, and arterial encasement.[1,2]

One of the major limitations of arteriography has been the detection of these hypovascular scirrhous malignancies, where no neovascularity or tumor stain can be identified. In such cases, arterial encasement may be the sole indicator of a malignant process. Veins, however, may be more sensitive than arteries in reflecting such involvement by contiguous tumors since they are thin walled, without a highly developed muscular coat.

This concept has proved helpful in the evaluation of malignancies in other organs. Buranasiri and Baum[3] have emphasized the value of venous abnormalities in evaluating pancreatic carcinoma, having no instance in their 50 cases in which arterial findings were present in the face of normal veins.

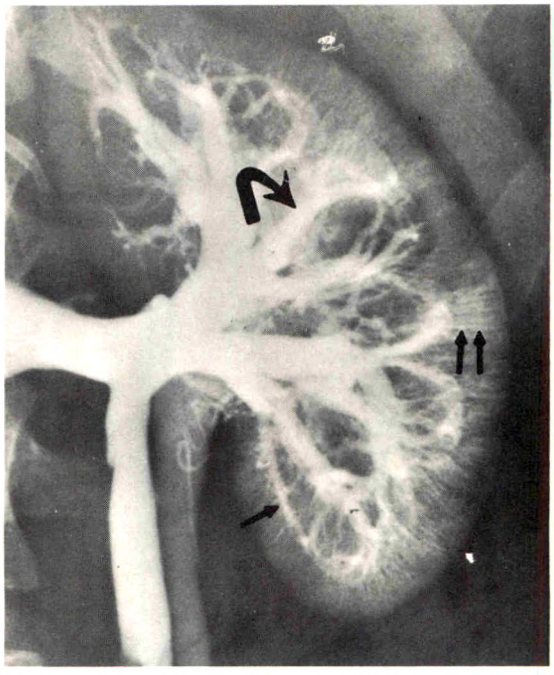

Fig. 1. Normal renal venogram. Note the excellent opacification of interlobar veins (curved arrow), arcuate veins (straight arrow), and intralobular veins (double arrows).

In many cases, major venous findings were present, with no detectable arterial changes, again suggesting that the venous abnormalities may occur earlier. We believe that the same reasoning is applicable to renal tumors as well. Furthermore, veins do not manifest the changes of atherosclerosis which may confuse the interpretation of visceral arteriography.

McDonald and Priestley,[6] in a review of 76 renal pelvic carcinomas, described occlusion of the main renal vein or one of its smaller branches in 26.3 per cent of their cases. Despite these impressive pathologic findings, there are few published descriptions of intrarenal venous involvement secondary to transitional cell carcinoma. Renert *et al.*[10] did report tumor thrombosis of the main renal vein in 3 cases of transitional cell carcinoma, making this diagnosis by inferior vena cavography. Their published illustrations do not demonstrate the intrarenal veins, however.

The diagnostic findings at selective renal

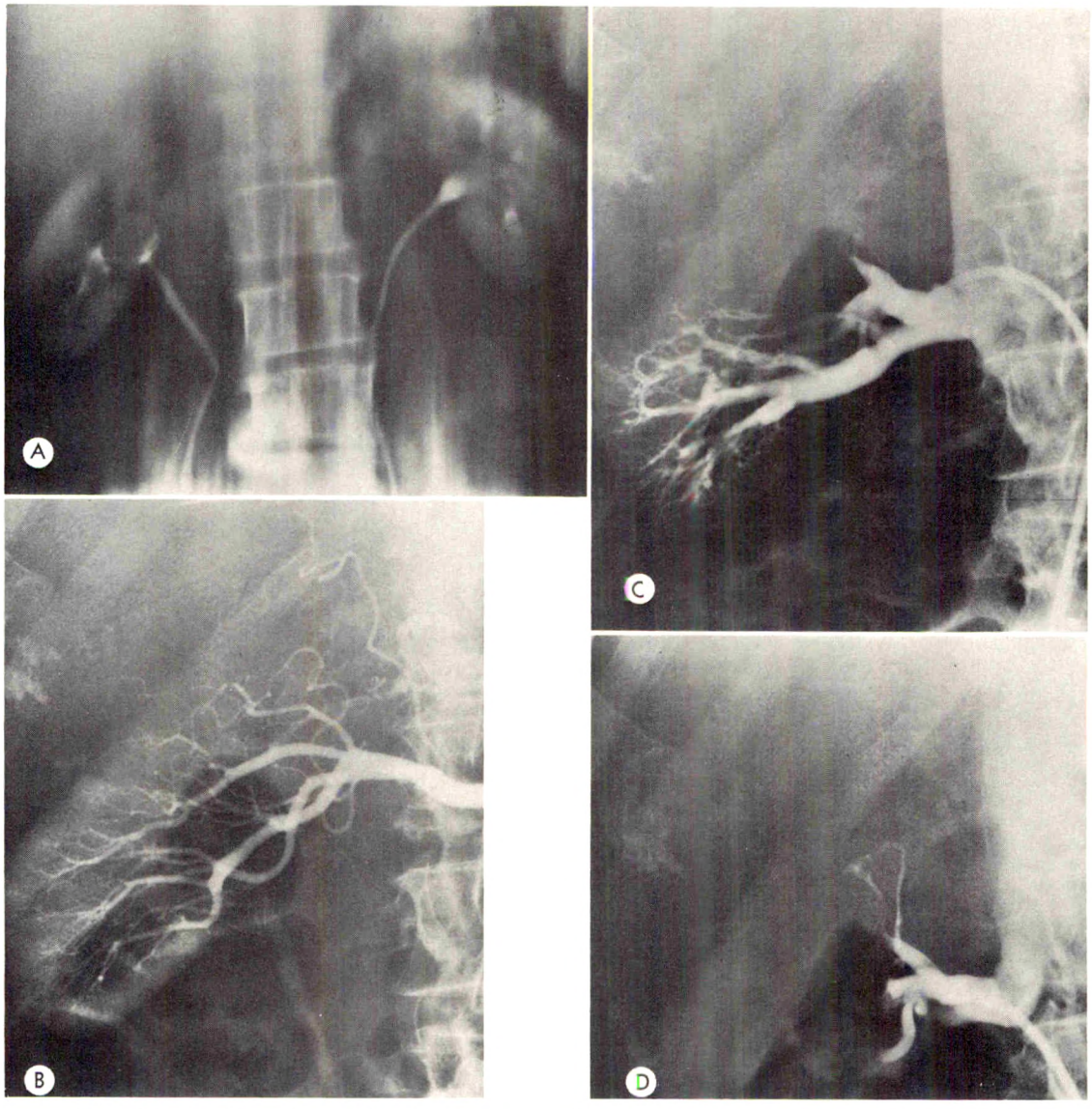

Fig. 2. Transitional cell carcinoma. (*A*) Intravenous pyelogram reveals a mass in the right renal pelvis. (*B*) Selective right renal arteriogram shows an avascular mass in the upper pole. (*C*) Selective right renal venogram demonstrates amputation of virtually the entire venous bed in the upper pole. (*D*) Selective injection into the stump of the encased vein confirms the extensive obliteration of the upper pole veins.

venography have been encasement and amputation of the intrarenal veins. Although filling of the renal venous bed may be virtually complete (Fig. 1), the simple demonstration of segmental nonopacification is not necessarily pathologic, and may be related to the presence of multiple veins, or may reflect incorrect catheter position. The catheter placement is, therefore, quite important with optimal position being at the division of the main renal vein into its segmental branches. A more peripheral catheter placement will result in overloading of the segments drained by the injected vein, with underfilling of the remaining segments. Furthermore, renal venous anatomy is subject to many variations, with the incidence of multiple vessels on the right side reported as high as 25 per cent, whereas on the left side, the incidence is strikingly

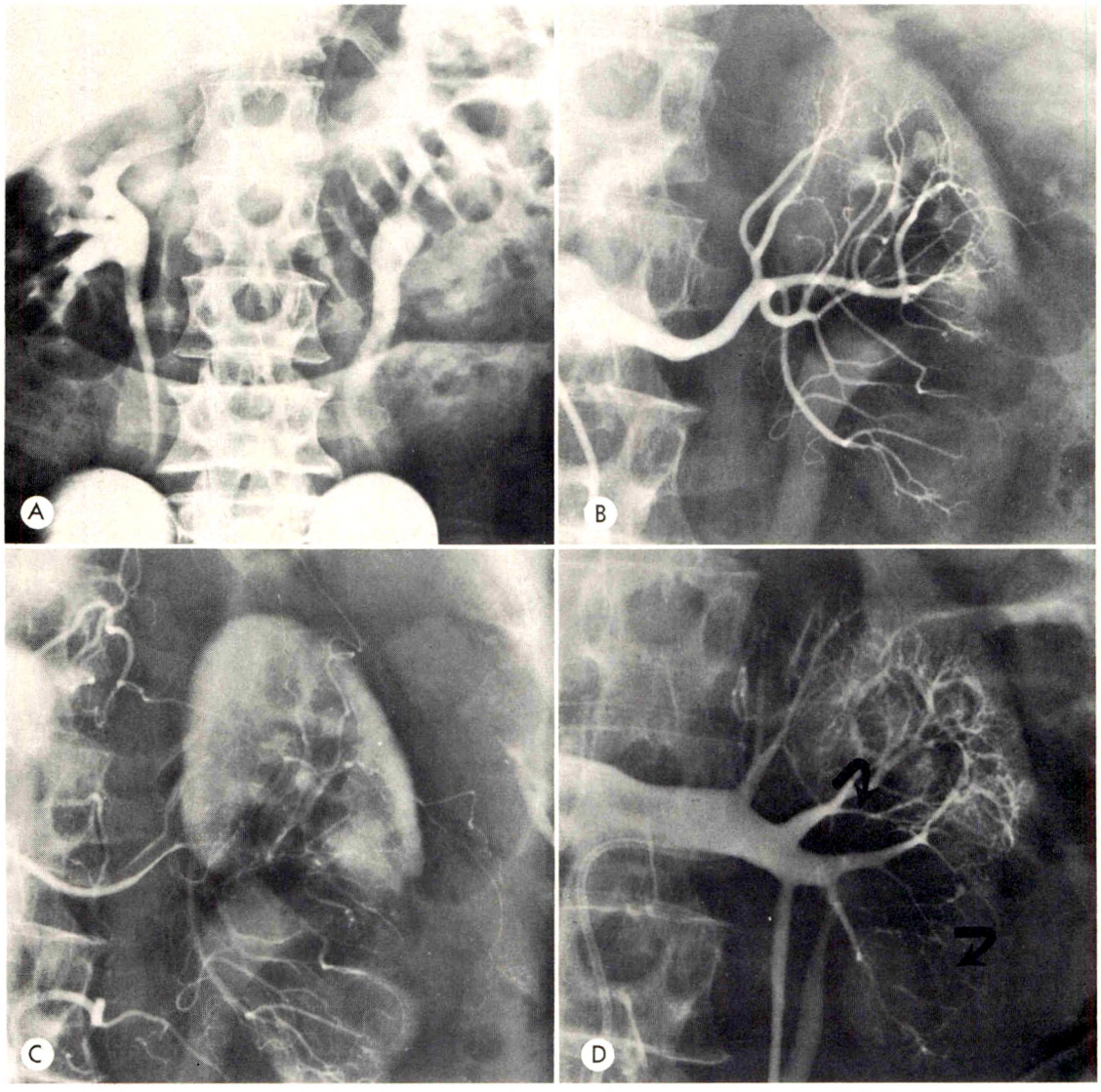

Fig. 3. Transitional cell carcinoma. (*A*) Intravenous pyelogram shows a mass involving the lower pole of the left kidney. (*B*) Selective left renal arteriogram demonstrates an avascular mass effect, but no encasement or neovascularity. (*C*) Later phase of *B* confirms the mass. No tumor stain is apparent. (*D*) Selective left renal venogram. Note the extensive encasement (curved arrows) of multiple veins in the lower pole.

lower, averaging approximately 1 per cent.[9]

Simple displacement and extrinsic compression of intrarenal veins may be seen with both benign and malignant processes. The more ominous findings of venous encasement (Fig. 2, *A–D*), and complete amputation (Fig. 3, *A–D*), suggest a malignant etiology. It is of interest that all of our patients had selective renal arteriograms with technically excellent magnification studies which failed to indicate the malignant nature as well as the extent of the neoplastic process. The unequivocal venous encasement and amputation indicated malignancy in all patients.

Although we have no such examples, we would predict that renal lymphoma involving the kidney would produce similar alterations in the venous anatomy. The histologic nature of the malignant lesion

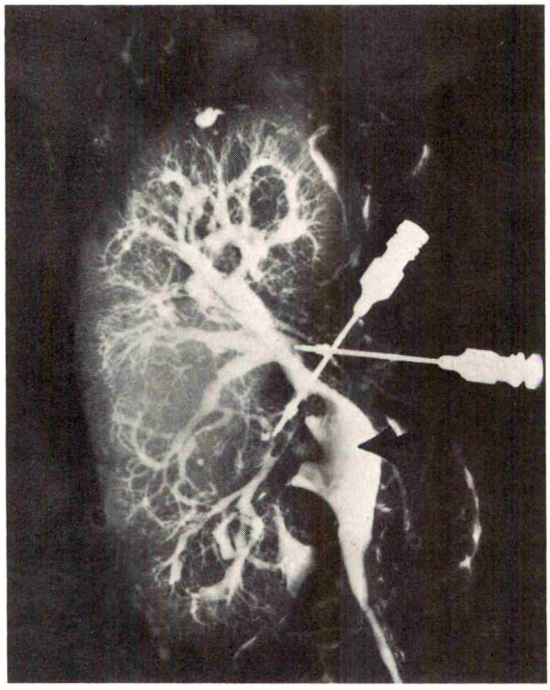

FIG. 4. Avascular hypernephroma (injection specimen). Contrast material has been injected into the main renal vein and has subsequently passed into the renal pelvis and proximal ureter. There are multiple amputated and encased veins in the mid portion of the specimen. Note the tumor indenting the lateral aspect of the renal pelvis (curved arrow).

cannot be determined by venography; in fact, we made the incorrect preoperative diagnosis of transitional cell carcinoma in 1 of our cases, when the final pathologic report indicated an avascular hypernephroma.

CONCLUSION

Selective renal venography is a simple, safe technique which can be easily performed at the time of diagnostic renal arteriography to help elucidate the nature of a renal mass lesion.

Venography is particularly indicated when the intravenous pyelogram demonstrates a mass lesion in a patient where the clinical suspicion of malignancy is high, and the findings at nephrotomography and renal arteriography are inconclusive.

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TRANSCATHETER EMBOLIZATION OF RENAL CELL CARCINOMA*

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TRANSCATHETER selective arterial embolization has been successfully utilized in a variety of clinical situations including central nervous system arteriovenous malformations and tumors,[4,9,12] gastrointestinal bleeding,[8,14,16,18] traumatic renal and pelvic bleeding[3,15] and epistaxis.[17]

Lalli *et al.*[10] first evaluated the feasibility of transcatheter renal infarction by various methods in experimental animals as a potential therapeutic measure. Similarly, Doppman *et al.*[5] utilized a silicone rubber preparation in experimental animals to obliterate the intraparenchymal vascular bed of abdominal organs. Lang[11] reported 20 hypernephromas managed by transcatheter infarction with radioactive gold seeds in combination with other treatment modalities. More recently, Almgård *et al.*[1] reported successful embolic occlusion of renal carcinomas with autologous muscle tissue.

At the present time a clinical trial is under way at the University of Texas M. D. Anderson Hospital and Tumor Institute to evaluate the efficacy of selective intra-arterial occlusion in the management of renal cell carcinoma. There are 3 clinical situations for which embolic occlusion of renal cancers have been performed: 1. preoperatively to reduce tumor vascularity for the purpose of making surgery technically more expedient; 2. therapeutic reduction of tumor bulk in inoperable cases, alone or in combination with other therapeutic modalities; 3. palliation of specific symptoms such as flank pain and/or hematuria.

This communication presents our experiences with transcatheter embolic occlusion of 12 hypernephromas.

TECHNIQUE

Embolization is usually performed at the conclusion of the diagnostic angiographic evaluation of the suspected renal tumor. A preshaped, thin-walled polyethylene catheeter (I.D. = 1.2 mm.; O.D. = 2.2 mm.) is utilized for the angiographic examination as well as the embolic occlusion. Most often, the original angiographic catheter has been used for the occlusion without exchanging for a different catheter shape. The catheter is advanced as far into the renal artery as possible to accomplish more selective embolization of the tumor and to avoid reflux of the embolic material into the aorta.

Surgical-type gelatin sponge (Gelfoam) has been utilized as the embolic material in all cases but one in which embolization was performed with autologous subcutaneous tissue. The Gelfoam is cut into multiple tiny pieces measuring up to 5 mm. or into rectangular strips about 5 mm. in width. Approximately 1 cc. of packed dry Gelfoam particles or a Gelfoam strip is placed into a 10 cc. syringe. Subsequently, about 8 cc. of normal saline is drawn into the syringe, and the combination is vigorously shaken. This allows thorough wetting of the Gelfoam to facilitate injection.

Embolization is performed in stages with careful fluoroscopic monitoring and interval angiographic runs if necessary. Approximately 1–2 cc. increments of the Gelfoam-saline mixture are injected. Test injections of contrast material follow each increment to continually assess the remaining vascularity of the tumor. Depending upon the vascularity of the tumor and size of the particles injected, large hypernephromas

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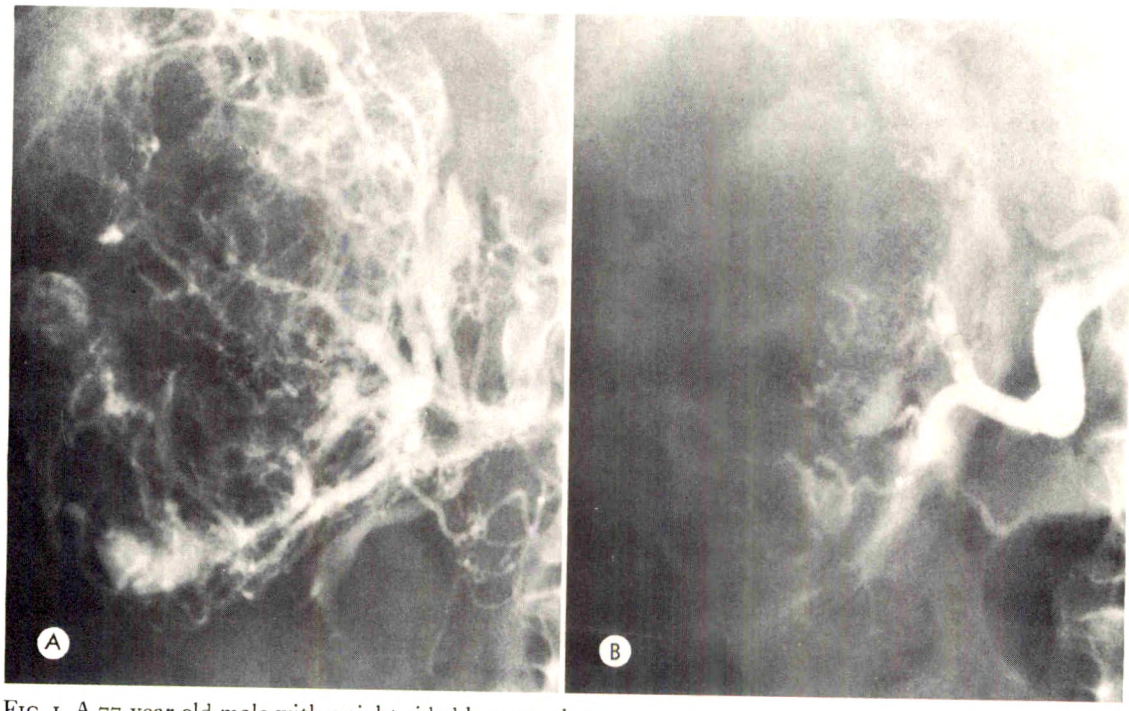

Fig. 1. A 77 year old male with a right-sided hypernephroma.

(*A*) Selective right renal arteriogram demonstrates a large hypervascular tumor with considerable laking of contrast material. (*B*) Selective injection following embolization with 2 Gelfoam sponges shows virtually total obliteration of the tumor vascularity with occlusion of the renal artery just past the first bifurcation.

may require up to 2 or 3 Gelfoam sponges (2×6 cm.) for total occlusion (Fig. 1, *A* and *B*).

CLINICAL MATERIAL

Arterial embolization has been performed in 12 patients with hypernephromas. The patients consist of 11 males and 1 female, ranging in age from 37 to 77 years. Six of the embolizations have been performed prior to surgery, and in the other 6 patients, the embolizations were for palliative and treatment purposes in otherwise inoperable situations. Four of the preoperative occlusions were performed on the day prior to surgery, while in the other 2 patients the embolizations occurred 2 days and 7 days prior to surgery.

RESULTS

Six of the patients have subsequently undergone nephrectomy using a transabdominal approach. In 4 of these cases, surgical removal of the kidney was judged to be dramatically simplified because of collapse of the usually engorged and fragile tumor veins. Concomitantly, there has been a reduction in the expected blood loss and operative time (Fig. 2, *A* and *B*). In addition, it was the subjective impression of the surgeons in several cases that the edema induced by the infarction tended to make tissue planes more distinct, thereby facilitating dissection of the tumor-laden kidney. In 1 case, surgical removal of the hypernephroma was felt to be improved, but not as obviously as in the other 4 cases. In the sixth patient, no real surgical benefit could be ascribed to the preoperative infarction. In this case, complete embolization of the tumor could not be accomplished safely because of a short main renal artery. In addition, there was supply to the tumor from the splenic artery, and this extrarenal

source of vascularity may have increased in the 7 day interval between the infarction and surgery.

One of the inoperable patients was embolized for relief of right-sided costovertebral angle pain (Fig. 3, *A* and *B*). The hypernephroma no longer visualizes on intravenous pyelography and the patient's symptoms have completely disappeared. Follow-up evaluations are as long as 10 months among the 6 patients with inoperable tumors that underwent occlusion. All but 1 patient are alive and doing well, but definitive progress information is incomplete at this time.

DISCUSSION

No permanent side effects have been directly attributable to the tumor occlusion. Specifically, none of the patients have developed sustained hypertension or hematuria. The most common clinical sequela following occlusion is flank pain which occurred in 11 of the patients. Eight of these patients required narcotics and/or sedation for relief. The pain usually begins during or at the conclusion of the procedure, but occasionally not until 1–2 hours after completion. In those patients not undergoing surgery on the following day, the pain gradually subsided from 12–96 hours following the occlusion. Most often, it lasted for about 48 hours. Eight of the patients developed fever which was usually in the 100°–101° F. range. Temperature elevation up to 103° F. was recorded in 1 patient. The fevers have not necessarily paralleled the associated flank pain and usually have subsided by 24–48 hours. Elevation of blood pressure from normotensive levels to 180/120 mm. Hg occurred in only 1 pa-

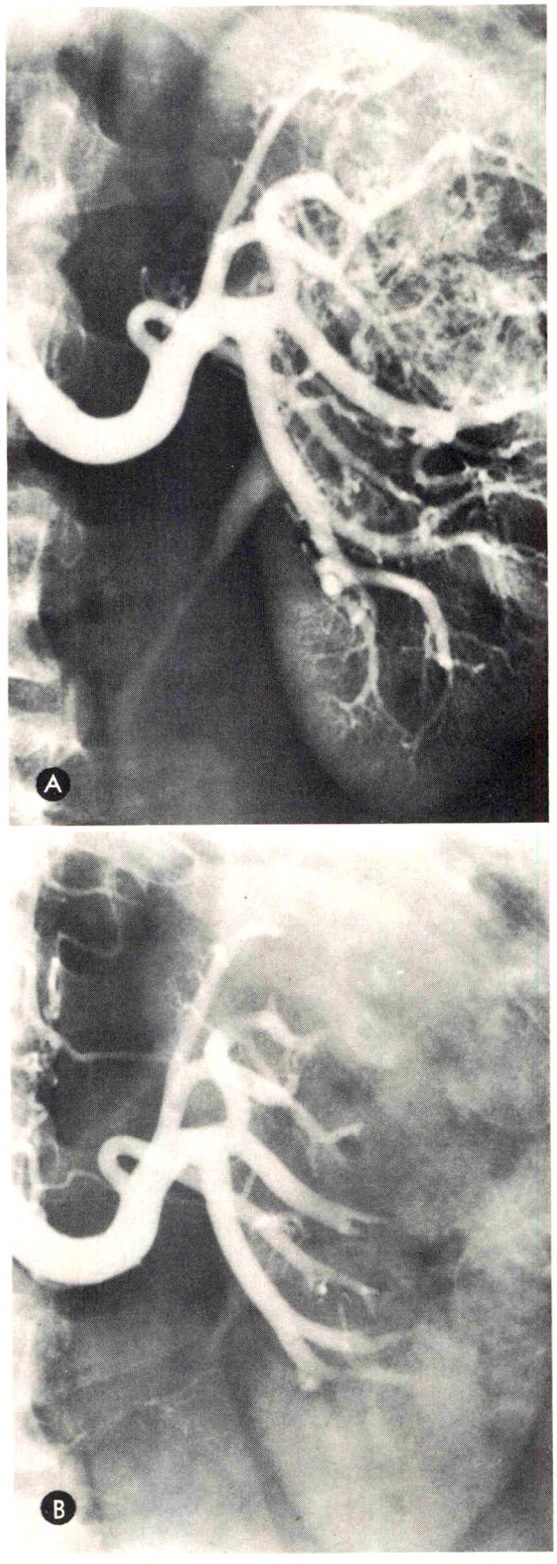

Fig. 2. A 56 year old male with a hypernephroma of the left kidney.

(*A*) Preoperative renal arteriogram demonstrates the typical appearance of a vascular hypernephroma. (*B*) Following Gelfoam embolization there is occlusion of the entire tumor vascularity.

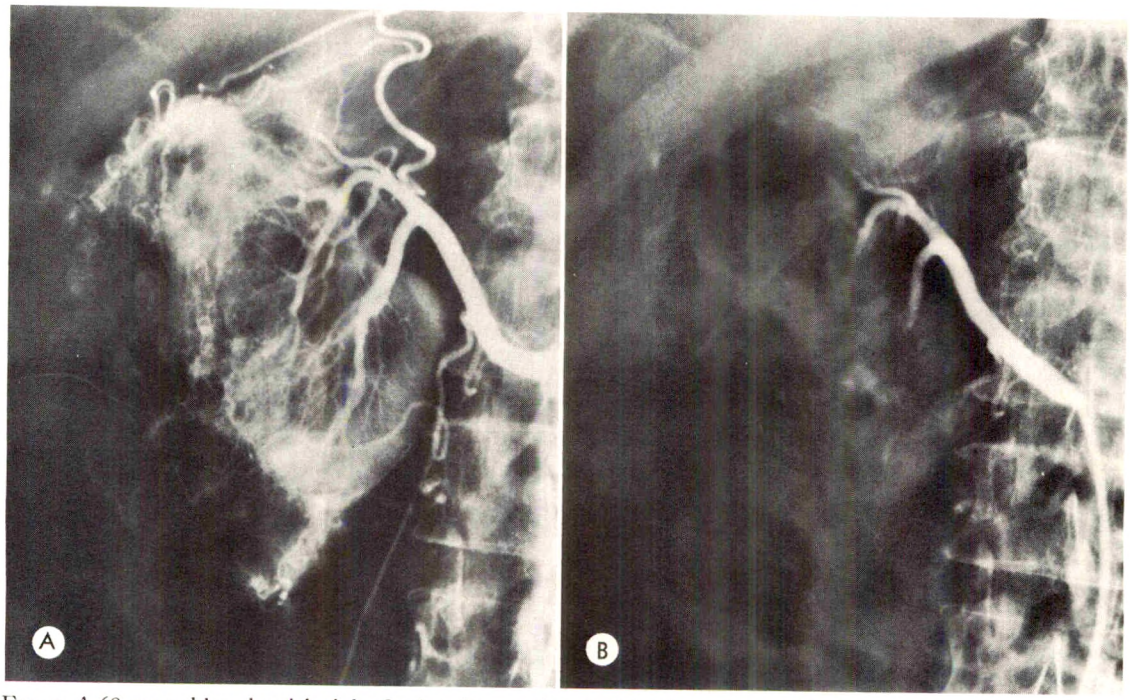

Fig. 3. A 68 year old male with right flank pain associated with a large inoperable hypernephroma.
(*A*) Right renal arteriogram demonstrates the partially vascular, necrotic hypernephroma. (*B*) Repeat injection following Gelfoam embolization shows total occlusion of the tumorous kidney. There was subsequent relief of symptoms.

tient, but gradually decreased back to normal in 24 hours. One 72 year old patient, who underwent embolization for an inoperable hypernephroma, had an uneventful, asymptomatic course for approximately 48 hours. Thereafter, mental confusion and decreased urinary output were noted. Serum creatinine gradually rose from normal to 17 mg. per cent. He succumbed of progressive renal failure in 20 days despite intensive medical management. Postmortem examination demonstrated acute tubular necrosis of the non-tumorous kidney with no evidence of emboli. It is felt that the contrast material load and dehydration following the procedure accounted for his clinical picture.

An obvious contraindication to renal tumor occlusion would be the technical inability to place a catheter deep into the renal artery, so that the embolic particles could be safely injected without reflux into the aorta. Clinical and/or radiologic evidence of chronic renal disease of the uninvolved kidney would also preclude embolization of a functioning cancerous kidney since renal failure might well ensue. This does not appear to have been the case in the previously mentioned patient with renal failure since pre-infarction renal function was normal and no pyelographic visualization of the neoplastic kidney was present. Three of the patients in this series had considerable arteriovenous shunting, but no pulmonary infiltrates were encountered, presumably because the emboli occlude small arteries proximal to the shunts.

In our clinical experience at the present time, Gelfoam is the most suitable embolic material for occlusion of renal tumors. The main disadvantage for autologous clot for this purpose is its relatively rapid lysis. Autologous subcutaneous tissue and muscle produce relatively permanent vascular occlusion, but the amount required to totally occlude a large hypernephroma makes this somewhat impractical. Gelfoam is readily available and injectable in various sizes. It

appears to provide much more permanent vascular occlusion than autologous clot alone. Studies are currently underway in our laboratory to assess the permanence of vascular occlusion with Gelfoam and its long term local and systemic effects. A variety of other materials for vascular occlusion are also currently being evaluated in our laboratory and by others.[6,13]

Pathologic specimens demonstrate that in addition to causing vascular obstruction itself, Gelfoam serves as a framework for additional thrombus formation. Histologic sections of occluded arteries have shown an intense acute arteritis characterized by large numbers of polymorphonuclear cells infiltrating the vessel wall and the immediate perivascular area (Fig. 4). Presumably, this represents a direct reaction to the intravascular Gelfoam.

Following tumor occlusion, patients are being followed with serial intravenous pyelograms as well as routine clinical and laboratory studies. Serial radiologic examinations are performed to follow any known pulmonary or bone metastases. Renal vein and systemic venous blood samples are being studied prior to and at regular intervals following the procedure for the effects of renal tumor embolization and renal infarction on rennin, erythropoietin, carcinoembryonic antigen, and immunoglobulins. Repeat arteriograms are planned in some patients not undergoing surgery to assess the angiographic status of the infarcted tumor.

Other potential uses exist for transcatheter embolization in the cancer patient. Intra-arterial embolization has been shown to be an effective nonsurgical means of controlling gastrointestinal or uterine bleeding in the cancer patient. This is especially true when it is the neoplastic tissue itself that is bleeding, as there is poor response to vasoconstrictors.[8] Preoperative occlusion of the arterial supply to hepatomas might also be useful in selected patients. Recently, we occluded the hepatic artery in a patient with a huge hepatoma involving only the right hepatic lobe. There was a 50 per cent

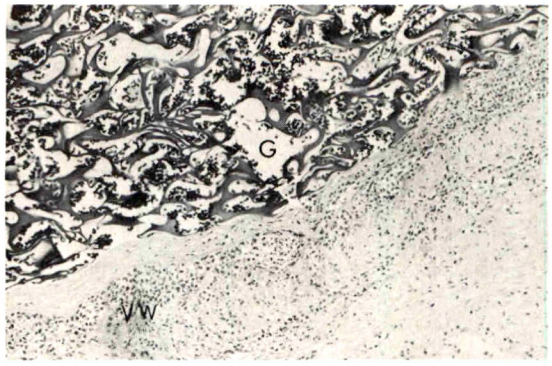

Fig. 4. Enlarged photomicrograph of a portion of an embolized intrarenal artery. The Gelfoam (G) forms a lattice-work in the artery lumen with red blood cells trapped in the interstices. Innumerable inflammatory polymorphonuclear cells are present in the vessel wall (VW) indicating arteritis.

reduction in the tumor size over a 5 week period. At this time, the lesion was felt to be more surgically manageable, but unfortunately, the patient expired during the operation. Similarly, hepatic metastases have been managed surgically with de-arterialization.[2,7] If this form of therapy continues to be promising, it might well be accomplished *via* transcatheter occlusion of the arterial supply rather than by surgical intervention. Another worthwhile area for experimental and clinical investigation would seem to be transcatheter attempts at splenectomy in patients with hypersplenism syndromes.

SUMMARY

Experiences with transcatheter embolic occlusion of 12 hypernephromas are presented.

Tumor occlusions were performed preoperatively in 6 of the patients to aid surgical management. In the 6 inoperable cases, embolizations were performed for palliation of specific symptoms and to reduce tumor size, usually in conjunction with chemotherapy.

Results of the preoperative embolizations are encouraging as surgical resections have been facilitated with decrease in operative times and blood loss. Follow-up data are

presently accumulating in the inoperable cases.

Pertinent technical considerations of tumor infarction and side effects of the procedure are discussed.

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STAGE I WELL DIFFERENTIATED ADENOCARCINOMA OF THE ENDOMETRIUM*

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THE treatment of well differentiated adenocarcinoma of the endometrium Stage I disease continues to be controversial. Total hysterectomy alone has given very good cure rates.[11] However, some patients are at risk for treatment failure. The risk has been related to the degree of muscle invasion and the presence of metastases.[1,14,15] Adjunct irradiation has been used to minimize the risk for treatment failure. The indications for radiotherapy and the proper method of delivery are in doubt.[2,6,11,14]

Proper treatment should encompass all the extent of tumor spread. The method of treatment is initially determined by the clinical stage. We assessed whether the clinical stage could be used to determine proper treatment by comparing the clinical stage to the pathologic stage. The effectiveness of surgical treatment alone and surgical treatment with adjunct irradiation was assessed with special regard to tumor recurrence and cause of death.

MATERIAL AND METHOD

Between 1966 and 1972, 112 patients with well differentiated adenocarcinoma of the endometrium Stage I disease were treated by total hysterectomy. The study group consisted of 88 patients initially staged I clinically and 24 patients staged I post hysterectomy. One hundred and eight patients had a total abdominal hysterectomy and bilateral salpingo-oophorectomy and 4 patients had a vaginal hysterectomy. Nine patients had preoperative irradiation delivering a minimum of 5,000 milligram hours with vaginal and intrauterine radium; 4 patients had postoperative irradiation with cobalt 60 teletherapy, delivering a minimum of 4,000 rads to the total pelvis.

The reliability of the histologic grading was assessed. One hundred and two patients had curettage and hysterectomy slides for review. The original histologic interpretations were atypical endometrial hyperplasia, adenocarcinoma *in situ* and well differentiated adenocarcinoma.[8] The review histologic interpretations were: atypical endometrial hyperplasia; well differentiated adenocarcinoma; and moderate differentiated adenocarcinoma.[3] We feel that the term adenocarcinoma *in situ* was inappropriate when used for the curettage specimens as many of the hysterectomy specimens had muscle invasion.

A comparison of the clinical stage with the anatomic extent of disease was made in the 88 patients staged I clinically. Excluded were patients with curettage findings of tumor extension into the endocervix and patients with pelvic findings suggesting node or ovarian metastases. Since preoperative irradiation can affect the anatomic findings, the 79 patients treated by hysterectomy alone were studied separately from 9 patients treated with preoperative irradiation.

Of the 24 patients staged I post hysterectomy, 15 patients had curettage specimens originally interpreted as atypical endometrial hyperplasia; 4 patients had only abnormal Papanicolaou smears and 5 patients had a hysterectomy without prior suspicion for carcinoma. All patients proved to have carcinoma limited to the corpus. These patients were included in the study

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TABLE I

COMPARISON OF ORIGINAL AND REVIEW HISTOPATHOLOGY

Original	Review		
Well Differentiated Adenocarcinoma	Well Differentiated Adenocarcinoma	Atypical Endometrial Hyperplasia	Moderately Differentiated Adenocarcinoma
102	94	3	5

in order to enhance the number of patients that could be evaluated for treatment response.

Treatment response was assessed from the recorded observations of tumor recurrence, metastases and cause of death.

RESULTS

The age range was 38 years to 84 years, with the median age 58 years. Ninety-one patients had abnormal uterine bleeding; 95 patients had the weight and length of the uterus recorded; 42 patients had leiomyomata; 68 patients used estrogens.

Histologic review showed 94 patients to have had well differentiated adenocarcinoma and 5 patients less well differentiated adenocarcinoma. Three patients had curettage and hysterectomy specimens that failed to show adenocarcinoma (Table I).

The clinical Stage I compared favorably to the surgical and hysterectomy findings. No patient was observed to have gross pelvic lymph node or abdominal metastases (Tables II; III; and IV). Most patients had noninvasive carcinoma or carcinoma invasive to less than one-third of the muscle thickness. Deeper invasion was infrequent. There was no relationship of the weight or length of the uterus to the extent of tumor invasion. The incidence and degree of muscle invasion was the same for patients with small and large uteri either with or without leiomyomata. Thirty patients had curettage specimens originally interpreted as adenocarcinoma *in situ*. Thirteen of these patients had invasive carcinoma.

Fifteen patients had curettage specimens interpreted as atypical endometrial hyperplasia; 6 patients had noninvasive carcinoma, and 6 patients had invasive carcinoma; 3 hysterectomy specimens failed to show carcinoma.

A total of 108 patients was followed for 1 to 7 years; 4 patients were lost to follow-up. Seventy-nine patients were followed for a minimum of 3 years—the high risk period for recurrence (Table IV).[4,17] No patient managed by either surgery alone or surgery with adjunct irradiation developed vaginal or pelvic recurrence, distant metastases or death from carcinoma.

DISCUSSION

Eighty per cent of our patients with well differentiated adenocarcinoma of the endometrium, Stage I disease presented with abnormal uterine bleeding. More than half

TABLE II

COMPARISON OF CURETTAGE TO HYSTERECTOMY FINDINGS FOR PATIENTS WITH CLINICAL STAGE I TREATED BY TOTAL HYSTERECTOMY

Curettage Findings	Hysterectomy Findings			
Well Differentiated Adenocarcinoma	No Residual Cancer	No Muscle Invasion	Superficial Muscle Invasion	Deep Muscle Invasion
79	17	31	28	3

Table III

COMPARISON OF CURETTAGE TO HYSTERECTOMY FINDINGS FOR PATIENTS WITH CLINICAL STAGE I TREATED BY PREOPERATIVE IRRADIATION AND TOTAL HYSTERECTOMY

Curettage Findings	Hysterectomy Findings			
Well Differentiated Adenocarcinoma	No Residual Cancer	No Muscle Invasion	Superficial Muscle Invasion	Deep Muscle Invasion
9	3	4	2	0

of the patients had used estrogens. Unopposed estrogen use can act as a stimulant to endometrial hyperplasia and may predispose to the development of malignancy.[16,17]

Surgery alone and surgery with adjunct irradiation have been advocated for well differentiated adenocarcinoma Stage I disease.[18] However, up to 15 per cent of patients managed by surgery alone have been reported to develop vaginal recurrence and up to 12 per cent death caused by cancer.[9,15,18] Adjunct irradiation has been advocated to prevent local recurrence and improve survival.[15] The value of adjunct irradiation has been questioned. The basis for conflicting reports may have been due to the assessment of patients with differences in socioeconomic status or in extent of disease.[4,5,9,13,17,18]

We limited our study almost exclusively to patients with curettage specimens interpreted as suspicious or diagnostic of well differentiated adenocarcinoma. Patients with tumor extension into the endocervix or patients with a pelvic examination suggestive of lymph node or ovarian metastases were excluded. The histologic interpretation of well differentiated adenocarcinoma was corroborated in the hysterectomy specimen of most patients. The corroboration was important as the clinical stage does not accurately predict the true extent of disease for patients with less well differentiated adenocarcinoma. Also, the prognosis is worse.[7,14]

Table IV

HYSTERECTOMY FINDINGS AND TREATMENT FOR PATIENTS FOLLOWED 3 YEARS

Hysterectomy Findings	Treatment	
	Surgery	Surgery and Irradiation
No Muscle Invasion	39	5
Muscle Invasion	31	4

None of our patients with well differentiated adenocarcinoma Stage I clinically proved to have carcinoma beyond the corpus. The carcinoma was usually noninvasive or invasive to less than one-third of the myometrium. Although approximately 4 per cent of patients with well differentiated adenocarcinoma Stage I disease have been reported to have pelvic node metastases, no gross pelvic lymph node metastases were observed in our patients.[10,14] The favorable clinical course of our patients suggests that the presence of occult pelvic lymph node metastases was unlikely.

Most of our patients were treated solely by a total hysterectomy and bilateral salpingo-oophorectomy. Seventy per cent of our patients were followed for a minimum of 3 years—the high risk period for tumor recurrence.[4,17] No tumor recurrences or deaths caused by cancer were observed. The excellent results may be unique to our Medical Center where patients are followed closely and operated upon early. Our patients did not have extensive disease.

We are still uncertain whether adjunct irradiation is necessary. We have not excluded its value in preventing late treatment failures. Therefore, at present we continue to use adjunct irradiation in patients with a predictable long life ex-

pectancy. We use vaginal and intrauterine preoperative irradiation, as this almost always encompasses the known and suspected extent of disease. Rarely would the operative findings show tumor spread that would require total pelvic irradiation. Postoperative irradiation can be used for patients when adenocarcinoma is found unexpectedly in the hysterectomy specimen.[6,8]

SUMMARY

The experience of 112 patients with well differentiated adenocarcinoma of the endometrium Stage I disease was reviewed. All patients had a total hysterectomy and bilateral salpingo-oophorectomy; 13 patients had adjuvant radiotherapy.

The clinical stage correlated well with the pathologic stage and could be used with confidence to determine proper treatment. Almost all patients had noninvasive or minimally invasive carcinoma. No patient had tumor extension beyond the corpus.

Total hysterectomy alone gave excellent results. No patient developed vaginal or pelvic recurrence, distant metastases or death caused by endometrial cancer. The possibility of late recurrence and metastases could not be excluded.

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ADENOCARCINOMA OF THE ENDOMETRIUM*

VAGINAL RECURRENCES AND MORTALITY

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THE records of 51 patients who died from adenocarcinoma of the endometrium of the uterus during the years 1960 to 1970 have been retrospectively reviewed.

Of the 51 patients, 11 could not be evaluated for our study because of initial presentation with carcinomatosis, or were patients who died before treatment was started or could be completed. The remaining 40 patients were treated with a combination of irradiation and TAHBSO.* Radiation therapy was used preoperatively by a combination of Heyman's capsules and vaginal ovoids, or postoperatively by a combination of external supervoltage therapy and/or radium vaginal molds. Preoperative external irradiation was not used.

The purpose of this report is to attempt to evaluate which patients are at high risk for vaginal recurrence, for pelvic recurrence, or distant metastases, and the manner of death, and to arrive at a recommendation for the management of the high risk patient.

MATERIAL AND METHOD

The records of 51 patients who died from adenocarcinoma of the uterus during the years 1960 to 1970 have been retrospectively reviewed. Eleven patients have been excluded because of advanced presentation, leaving 40 patients as the basis for this study. The pathologic slides of these 40 patients have been reviewed, and an evaluation has been made of the degree of differentiation of the tumor. The dilatation and curettage specimens have been reviewed for grading of the tumor, and the TAH† specimen for depth of myometrial invasion. Those patients with vaginal recurrence have been documented, and correlated with the degree of differentiation, depth of myometrial invasion, and type of irradiation. The tissue specimens were graded histologically into well differentiated, moderately differentiated, and undifferentiated. Upon further study, it could be seen from a clinico-histologic standpoint that 2 groups could be identified. Well and moderately differentiated specimens formed one group, and undifferentiated lesions the second group.

During the years 1960 to 1970, the following treatment protocol was used for endometrial carcinoma:

1. *Small uterus* (8 cm. depth or less)
   TAHBSO followed by Burnett Radium mold of 20+20 mg.
   Radium × 50 hours = 2,000 mg./hr. given 6 weeks postoperatively. The dose to the vaginal mucosa ranged from 4,210–8,160 rads at the surface depending on the diameter of the mold. Most patients have received 5,000 rads.
2. *Uterus* greater than 8 cm. depth
   Heyman radium capsules to fundus (4,000 mg./hr. total)
   Fletcher ovoids to vaginal vault (2,000 mg./hr. total)
   TAHBSO 6 weeks following radium.
3. Postoperative radiation therapy was reserved for tumor which had spread outside the uterus, to pelvic lymph nodes, or adjacent organs.

RESULTS

Of the 40 patients reviewed, 28 were classified as demonstrating well or moderately differentiated lesions (Fig. 1). Thirteen of these 28 were shown on TAHBSO

* Total abdominal hysterectomy and bilateral salpingo-oophorectomy.

† Total abdominal hysterectomy.

* Presented at the Seventy-fifth Annual Meeting of the American Roentgen Ray Society, San Francisco, California, September 24–27, 1974.

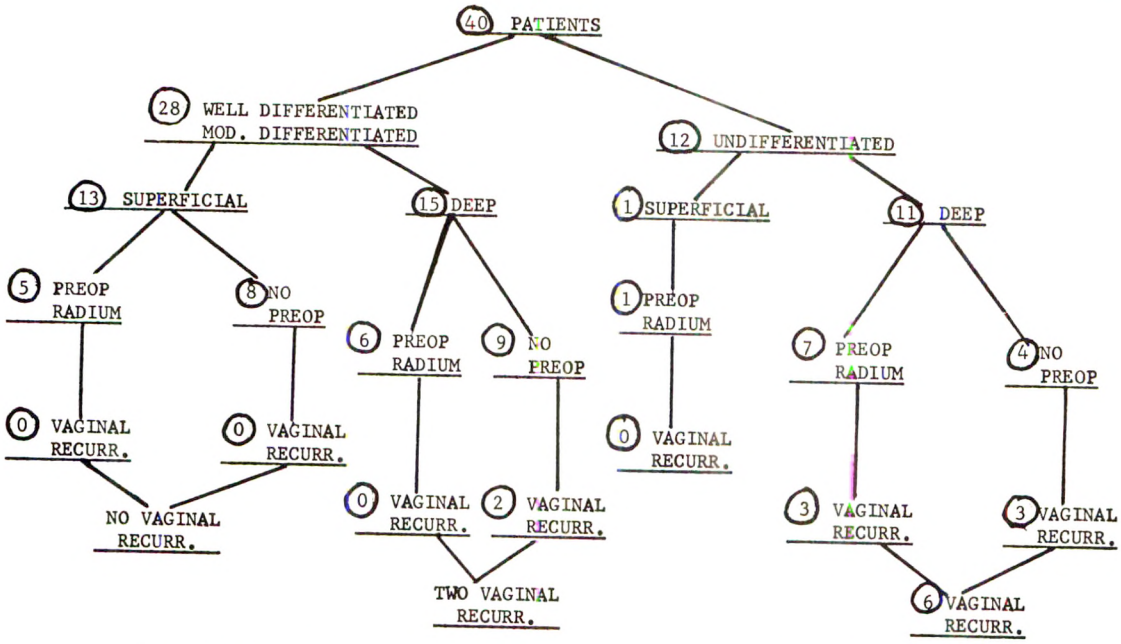

FIG. 1. Endometrial carcinoma—grading, depth of myometrial invasion, radiation therapy, and vaginal recurrences.

to have lesions which superficially invaded the myometrium of the uterus. Of these 13 patients, 5 had preoperative curietherapy and 8 had no preoperative curietherapy. Burnett molds were used postoperatively. There were no vaginal recurrences in the 13 patients with superficial invasion of the myometrium. The pattern of recurrence in patients with superficial invasion of the myometrium was essentially distributed within the abdomen, and distantly to lung, liver, brain and bone. Very few pelvic recurrences were noted (Table 1).

Deep invasion of the myometrium was present in 15 of 28 patients classified as having well or moderately differentiated lesions. Six of these 15 had preoperative curietherapy with no vaginal recurrences. Nine of the 15 had no preoperative irradiation, and of these two developed vaginal recurrences. The pattern of recurrence in patients with deep invasion was distributed mainly within the abdomen, and distantly to lung, liver, brain and bone. A moderate amount of pelvic recurrences was also noted (Table 1).

TABLE I

ENDOMETRIAL CARCINOMA—MORTALITY AND VAGINAL RECURRENCES

	Patients	Vaginal Recurrences	Pelvic Recurrences	Abdominal Recurrences	Lung, Liver, Brain, Bone
Well Differentiated Moderately Differentiated	28	2	6	23	15
Undifferentiated	12	6	5	10	9
Superficial	14	0	3	11	12
Deep	26	8	7	17	11

Twelve of 40 patients were classified histologically as having undifferentiated lesions (Fig. 1). Only 1 patient with an undifferentiated lesion had superficial myometrial invasion. This patient had preoperative curietherapy and did not develop vaginal recurrence. Eleven of the 12 undifferentiated lesions demonstrated deep myometrial invasion. Seven of these 11 patients had preoperative curietherapy and 3 developed vaginal recurrences. Four of the 11 had no preoperative curietherapy, and 3 of these developed vaginal recurrences. Of the 11 patients with deep myometrial invasion and undifferentiated lesions, 6 developed vaginal recurrences. Regarding the pattern of recurrence, the patients with undifferentiated lesions had a high incidence of pelvic recurrence, abdominal recurrence, and distant metastases to lung, liver, brain and bone (Table 1).

DISCUSSION

From our study, and a review of the literature,[1–7] there are 2 groups of patients at risk for the development of vaginal recurrence.

The first group consists of those patients who, after TAHBSO, are found to have deep myometrial invasion. We feel that these patients, after TAHBSO, should have more intensive postoperative irradiation than we used. The volume at risk is the entire pelvis and not just the vaginal apex in the majority of our patients. We intend to treat these patients with whole pelvis supervoltage irradiation to 5,000 rads total, at the rate of 800 rads per week and 4 fractions per week, and follow this with additional irradiation to the vaginal cuff of 2,500 rads by transvaginal technique. At 5,000 rads whole pelvis postoperatively, there is risk of small bowel morbidity, especially in obese patients. The transvaginal irradiation can be given with minimal morbidity. Regarding patterns of recurrence for patients with deep myometrial invasion, consideration should be given to the use of progestins as soon as there is early evidence of abdominal recurrences, or distant metastases to lung, liver, brain and bone.

The second group of patients at risk for development of vaginal recurrences are those with undifferentiated lesions. These patients in our series still develop vaginal recurrences with our method of preoperative curietherapy, and are subject to a high incidence of pelvic, abdominal and distant metastases. After dilatation and curettage, we plan to treat these patients with whole pelvis supervoltage irradiation to 5,400 rads, at 800 rads weekly, 4 fractions per week, followed by TAHBSO in 4 to 6 weeks. Following healing of the vaginal cuff, no additional irradiation is planned. In view of the high incidence of pelvic, abdominal and distant metastases, early consideration for the use of progestins should be made when there is evidence of recurrent disease. These patients are candidates for elective chemotherapy when more effective agents are available than we presently have.

SUMMARY

1. Patients with deep myometrial invasion are at risk for vaginal and/or pelvic recurrence. More intensive postoperative irradiation is indicated.

2. Patients with undifferentiated lesions are at high risk for vaginal and/or pelvic recurrence. These patients should have more intensive preoperative irradiation than we have previously given, to reduce the risk of local recurrence.

3. Both groups of patients are at risk for development of pelvic, abdominal and distant metastases. Early use of progestins when there is evidence of recurrent disease is recommended. Elective chemotherapy should be considered when a more effective agent is available than we presently have.

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COMBINED IRRADIATION AND CHEMOTHERAPY FOR SARCOMAS OF THE PELVIS IN FEMALES*

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PELVIC sarcomas are usually lethal and are difficult to cure even when small or localized. Although most authors have reported a fatal outcome for patients with these tumors, several recent articles suggest that many patients with localized uterine sarcomas can be cured with a combination of irradiation followed by surgery.[2,5,9] When the tumors are extensive or spread locally, they often metastasize to distant sites.

During the past 15 years, several chemotherapeutic drugs have proved their value in the care of patients with advanced untreatable sarcomas. More recently, combinations of these drugs have been found to be more successful than the drugs used individually.[7,8] As more experience has been gained in chemotherapy for sarcomas, it seemed logical to attempt to improve the results of this therapy by combining cytotoxic drugs with irradiation.

This report describes our experience with a combination of irradiation and chemotherapy in the treatment of patients with pelvic sarcomas.

MATERIAL AND METHODS

Thirty-eight patients with advanced, recurrent, or metastatic sarcomas arising in the pelvis have been treated with combination irradiation and chemotherapy by the Gynecology Department and the Radiotherapy Department at The M. D. Anderson Hospital between the years 1965 and 1973. The patients vary in age from 2 years to 76 years. Four of the patients were under 6 years of age, 5 were between 6 and 40, 5 were over 60, and 24 were between the ages of 40 and 60 when treated.

Twenty-four of the patients had sarcomas arising in the uterus, 4 patients had sarcomas arising in the ovary, 3 patients had sarcomas arising in the vagina, 3 had retroperitoneal sarcomas, 1 patient had a sarcoma arising in the cervix, 1 had a sarcoma arising in the perineum, 1 had a sarcoma arising in the bladder, and 1 had a sarcoma arising in the fallopian tube (Table 1).

TABLE I
ORIGIN OF SARCOMAS

Tumor Site	No. of Patients
Uterus	24
Ovary	4
Vagina	3
Cervix	1
Retroperitoneum	3
Perineum	1
Bladder	1
Fallopian tube	1
Total	38

Eighteen patients had mixed mesodermal sarcomas, 8 had leiomyosarcomas, 3 had embryonal rhabdomyosarcomas, 3 had endometrial stromal sarcomas, 2 had alveolar rhabdomyosarcomas, and 1 patient each had sarcoma botryoides, neuroblastoma, primitive neurogenic tumor, and neurofibrosarcoma (Table II).

All patients had surgery at some time during their treatment, but in several, this consisted of only a biopsy and in none was it thought to be curative. The irradiation that each patient received was individualized to her problem and to her tolerance to the combined treatment. In general, patients with advanced pelvic tumors or with metastatic sarcomas outside the abdominal

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TABLE II

RESULTS OF TREATMENT BY HISTOLOGY

Histology	No. of Patients	No. NED	Mo. NED
Mixed mesodermal	18	4	26, 34, 48, 56
Leiomyosarcoma	8	7	10, 26, 26, 29, 33, 34, 40
Embryonal rhabdomyosarcoma	3	2	60, 72
Endometrial stromal	3	0	—
Alveolar rhabdomyosarcoma	2	0	—
Sarcoma botryoides	1	0	—
Other sarcomas	3	1	65
Total	38	14	

cavity received 5,000 rads to the pelvis through parallel opposed anterior and posterior portals on a 22 mev Betatron. Patients with evidence of intraperitoneal spread, either pelvic or intra-abdominal, received 2,600 to 2,800 rads on a cobalt 60 unit to the whole abdomen by the moving strip technique, shielding the liver with 1 half-value layer of lead to both front and back, and shielding the kidneys from the back with 2 half-value layers of lead. All but one patient who received the whole abdominal irradiation by the moving strip technique received 2,000 rads additional irradiation to the pelvis through parallel opposed anterior and posterior portals from a 22 mev Betatron. Two patients received only a single treatment of 1,000 rads through anterior and posterior portals as palliative treatment combined with chemotherapy, and one patient received 7,000 rads irradiation to the pelvis through anterior and posterior parallel opposed portals.

Five patients received intra-arterial vincristine while receiving irradiation. In 4 of these patients, the infusion catheter was placed in the lower aorta below the origin of the inferior mesenteric artery, and one patient had catheters placed in both hypogastric arteries at laparotomy. Twenty-three patients received systemic vincristine during their irradiation therapy. Nine patients received both vincristine and actinomycin-D during their irradiation therapy. Twenty-one patients received a combination of vincristine, actinomycin-D, and cytoxan (VAC) after their irradiation was completed (Table III).

The patients who received intra-arterial chemotherapy received .8 to 1 mg of vincristine daily for 5 of 7 days each week for either 4 or 5 weeks during their irradiation therapy. The other patients who received combined systemic chemotherapy and irradiation can be divided into 2 groups: One group of patients who were treated aggressively because of very malignant lesions, such as mixed mesodermal sarcomas or embryonal rhabdomyosarcomas, received vincristine, 1.5 mg per meter square body surface area, each week for 10 to 12 weeks and actinomycin-D .5 mg per day for 5 days every 4 weeks while receiving irradiation. Another group of patients with less malignant lesions, such as leiomyosarcomas or endometrial stromal sarcomas, received vincristine, 1.5 mg per meter square body surface area, weekly for 10 to 12 weeks while receiving irradiation.

RESULTS

Four of 18 patients with mixed mesodermal sarcomas were free of disease at 26,

TABLE III

VAC

Vincristine 1.5 mg/M² B.S.A. every wk × 10–12 wk IV
Actinomycin D .5 mg/d × 5d every 4 wk IV
Cyclophosphamide 5–7 mg/kg/d × 5d q 4 wk IV
Treatment repeated every 4 wk as tolerated for 2 yr

34, 48, and 56 months (Table II). Seven of 8 patients with leiomyosarcomas of the pelvis treated with chemotherapy and irradiation are alive and well without evidence of recurrent sarcoma at 10, 26, 26, 29, 33, 34, and 40 months. Two patients with embryonal rhabdomyosarcomas are alive and well without evidence of recurrent sarcoma at 60 and 72 months. One patient with a neuroblastoma is alive and well without evidence of disease at 65 months. Three patients with endometrial stromal sarcoma, 2 patients with alveolar rhabdomyosarcoma, 1 patient with sarcoma botryoides, and 1 patient with neurofibrosarcoma and 1 with a primitive neurogenic sarcoma are dead of their sarcomas after treatment with combined irradiation and chemotherapy.

Among the 4 patients with mixed mesodermal sarcomas who are alive and well without evidence of recurrent sarcoma, 1 had advanced local disease when her treatment was begun (Table IV). This patient had a large mixed mesodermal sarcoma of the ovary which was adherent to the left pelvic wall and was dissected free of the iliac vessels and the left ureter at the time of original surgery. Including 12 patients treated at The M. D. Anderson Hospital and a review of the recent literature, only 4 patients out of a total of 94 patients with mixed mesodermal sarcoma of the ovary are alive and well without evidence of disease more than 5 years after treatment.[1,3,4,6]

Two patients with recurrent mixed mesodermal sarcomas are alive and well without evidence of disease. Both of these patients had mixed mesodermal sarcomas of the uterus—one recurrent at 21 months after abdominal hysterectomy and bilateral salpingo-oophorectomy, and the other, at 9 months after an abdominal hysterectomy and bilateral salpingo-oophorectomy. Both patients had recurrent tumor in the upper vagina and pelvis. One patient with metastatic mixed mesodermal sarcoma of the uterus is alive and well without evidence of disease. This patient had a total abdominal hysterectomy and bilateral salpingo-oophorectomy as the initial treatment for her sarcoma. At surgery she was found to have a large uterus with metastatic mixed mesodermal sarcoma in the left parametrial tissue at the margin of resection and metastatic mixed mesodermal sarcoma in her left ovary. The omentum was adherent to the uterus and ovary at the time of the original surgery.

Seven of 8 patients with leiomyosarcomas treated with combined irradiation and chemotherapy were alive and well without evidence of disease. One patient had a subtotal hysterectomy and bilateral salpingo-oophorectomy at another hospital before being referred to M. D. Anderson Hospital

TABLE IV

RESULTS OF TREATMENT BY HISTOLOGY AND TUMOR STATUS

Histology and Status	No. of Patients	No. NED
Mixed mesodermal sarcoma		
Advanced local	5	1
Recurrent	8	2
Metastatic	5	1
Total	18	4
Embryonal rhabdomyosarcoma		
Advanced local	2	1
Recurrent	0	0
Metastatic	1	1
Total	3	2
Leiomyosarcoma		
Advanced local	1	1
Recurrent	1	1
Metastatic	6	5
Total	8	7
Endometrial stromal sarcoma		
Metastatic	3	0
Total	3	0
Other sarcomas		
Advanced local	3	1
Recurrent	1	0
Metastatic	2	0
Total	6	1

for treatment. One patient had recurrent leiomyosarcoma of the uterus 8 years after having a vaginal hysterectomy for a leiomyosarcoma. The recurrent sarcoma involved the pelvic peritoneum and both tubes and ovaries. Five patients were found to have metastatic leiomyosarcoma at the time of their initial surgery. One had metastatic tumor in her lungs and the other four had metastatic tumor in the pelvis or the abdomen.

Two of 3 patients with embryonal rhabdomyosarcomas were alive and well without evidence of disease after receiving combined irradiation and chemotherapy. At the time of her original treatment, one of these 2 patients had advanced local tumor involving the cervix, with metastasis to the pelvic wall nodes. The other patient had an embryonal rhabdomyosarcoma arising in the broad ligament with metastasis to the pelvic peritoneum.

One patient with a neuroblastoma that was discovered at the time of a cesarean section because of obstructed labor had advanced non-resectable local disease involving the posterior retroperitoneal space of the pelvis and extending up to the lower aorta and vena cava. She is alive without evidence of disease after treatment with combined irradiation and chemotherapy.

In addition to these 14 patients who are at present without evidence of disease, 7 other patients had good local control of their pelvic sarcomas with combined treatment, but died of metastatic sarcoma or complications of treatment. Four of these patients had mixed mesodermal sarcomas; 1 had alveolar rhabdomyosarcoma, 1 had embryonal rhabdomyosarcoma, and 1 had sarcoma botryoides.

COMPLICATIONS

Complications associated with this combined treatment have been severe (Table v). Five patient's deaths were directly related to their treatment. All 5 of these patients had severe vincristine toxicity with profound muscular weakness and respiratory impairment as a result of the neuromuscular toxicity. This weakness lead to respiratory failure and inability to cough, resulting in pneumonia and finally death. Two of the patients had tracheostomies because of their inability to cough and clear their trachea of secretions. One was maintained for more than a week on the respirator because of her breathing difficulties and her low PO_2.

One of the patients who had severe respiratory difficulties and finally died of this complication also had cardiac toxicity. She had a cardiac arrhythmia and tachycardia which was treated with lidocaine, procainamide, propanolol, and digitoxin.

Eight patients had rectal bleeding following treatment. Several of these patients had had treatment first to the pelvis followed by treatment to the entire abdomen by the moving strip technique. With this combination of treatment given in this order, they would receive as much at 4,800 rads to the lowest strip in the pelvis over a period of $3\frac{1}{2}$ weeks.

Three patients had hematuria requiring blood transfusions following completion of their treatment. Nine patients had severe peripheral neuropathy which confined them to a wheel chair for a short period of time. Several have had to use a cane or walker for as long as a year after completing their treatment. All have subsequently recovered from the peripheral neuropathy.

Five patients had severe hematological toxicity as a result of their chemotherapy following irradiation. All 5 of these patients required hospital admissions for severe

TABLE V

COMPLICATIONS OF TREATMENT

Complications	No. of Patients
Death	5
Rectal bleeding	8
Hematuria	3
Severe peripheral neuropathy	9
Severe hematological toxicity	5
Respiratory weakness	5
Ileus requiring hospitalization	2
Bowel injury requiring surgery	2

leukopenia with fever, and were treated for sepsis with high dose intravenous antibiotics. Two patients had severe ileus associated with their treatment, requiring hospitalization because of pain and cramps.

Two patients have developed intestinal injuries requiring corrective surgery as a result of their treatment. One patient required a bypass of her distal ileum because of obstruction of her terminal ileum, and a colostomy because of sigmoidal obstruction. She then developed a fistula from her ileum to colostomy site and required 3 intestinal operations because of additional fistulae and recurrent obstruction.

DISCUSSION

The intense treatment that these patients received requires close support of and cooperation between the radiotherapist, chemotherapist, and surgeon. All of these patients had advanced disease and all or almost all could have been expected to die of their sarcoma with conventional treatment with either chemotherapy or irradiation therapy alone.

Possibly all of the 5 deaths could have been prevented if the respiratory difficulties had been recognized and the vincristine therapy discontinued. This is a rare complication of high dose vincristine therapy.[10] Four of the 5 patients who developed severe respiratory difficulties and died were over 55 years of age. Three of the 5 patients with severe respiratory difficulties had bowel injuries with rectal bleeding.

Two patients had their treatment stopped because of severe toxicity. One of these patients who had an embryonal rhabdomyosarcoma survived for another 16 months and possibly might have been cured if her treatment had been continued. The one patient with a leiomyosarcoma who is not surviving had her treatment stopped before it was completed and was allowed to return home to rest. She never returned for additional treatment and died at home 5 months later. This patient had an initial good response to her treatment and possibly would have benefited from additional treatment.

One patient received palliative irradiation treatment only, consisting of 1,000 rads through 15×15 cm parallel opposed anterior and posterior portals in a single day. This patient had pulmonary metastasis when her treatment was first started. She had complete disappearance of her pelvic tumor with this treatment. After 5 months of chemotherapy, she failed to return to the clinic. She survived another 5 months at home before dying of metastatic sarcoma.

Twenty of the 38 patients in this study required 31 hospitalizations for supportive care during their combined irradiation and chemotherapy treatment.

SUMMARY

Thirty-eight patients with advanced, recurrent, or metastatic pelvic sarcomas were treated with combined irradiation and chemotherapy. Fourteen of these patients are presently alive and well without evidence of disease for 10 to 79 months following completion of their therapy.

The complications of this combined therapy have been severe, but few, if any, of these patients could have been expected to live with conventional therapy with either chemotherapy alone or irradiation therapy alone. A decrease in the dosage of vincristine would have prevented several of the deaths.

A change in order of administering whole pelvis and whole abdomen irradiation combined with chemotherapy possibly will prevent some of the bowel injuries associated with this treatment.

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RESULTS OF SURGICAL AND RADIATION THERAPY IN THE TREATMENT OF LIPOSARCOMA ARISING IN AN EXTREMITY*

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THE therapeutic approach to sarcomas of an extremity has interested surgeons and radiation therapists for several decades. Complete surgical extirpation of these tumors is often difficult because of proximity to neurovascular structures, large size and difficulty of obtaining a wide margin of uninvolved tissue. Amputation is frequently resorted to in these instances, but a disconcertingly high proportion of patients develop distant metastases after the loss of a functioning extremity. Among the various types of soft tissue sarcomas, liposarcoma is known to be one of the most radiosensitive.[3–6] A combined surgical and radiotherapeutic approach to the management of these tumors is therefore likely to be particularly advantageous, both in terms of tumor control and of obviating the need for amputation in otherwise indicated cases. At Memorial Sloan-Kettering Cancer Center such an approach has been employed intermittently over the years as dictated by the service policy, clinical setting and individual preference of the attending physicians.

It seems appropriate, therefore, to review our experience with the treatment of these tumors, with special emphasis on those treated by combined surgery and radiation therapy.

MATERIAL AND METHOD

Between 1949 and 1967 a total of 82 patients with potentially curable liposarcoma arising in an extremity were treated at Memorial Sloan-Kettering Cancer Center. Twenty-two additional patients were seen initially with distant metastases; these were excluded in computing the survival and recurrence rates of the curable cases. Another 9 patients were also excluded because of loss to follow-up or death unrelated to liposarcoma within 5 years of therapy. A histologic diagnosis of liposarcoma, either made or confirmed in our Pathology Department, was available in all cases.

Forty-nine patients were male and 33 were female. The age ranged from 16 to 75 years, with a median of 49 years. Table 1 gives the sites of origin of the tumor. Sixty-eight tumors were in the lower extremity and 14 were in the upper extremity. Twenty-nine previously untreated patients received primary therapy at Memorial Sloan-Kettering Cancer Center, while 53 came after one or more recurrences had developed following previous treatment at other institutions.

TABLE I

SITE OF ORIGIN OF LIPOSARCOMA

Upper extremity (14)	
Shoulder	3
Axilla	4
Arm	3
Elbow	1
Forearm	2
Hand	1
Lower extremity (68)	
Groin	9
Thigh	50
Leg	4
Knee	1
Popliteal	4
Total	82

* Presented at the Fifty-sixth Annual Meeting of the American Radium Society, Maui, Hawaii, April 21–25, 1974.
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SURGICAL TREATMENT

Wide resection of soft parts encompassing the tumor[2] was carried out in the majority of patients (50 cases). In many instances, whole muscle groups from origin to insertion were resected *en bloc* without exposure of the tumor, taking cognizance of the intrafascial spread[1] and occasional multifocal origin of these neoplasms.[7] Amputation or major extremity disarticulation was performed in 32 cases. The main indications for amputation were difficulty of obtaining adequate margin by soft part resection and clinically suspected involvement of the neurovascular bundle.

RADIATION THERAPY

Radiation therapy was administered to 29 patients. It was given with curative intent and adjunctively with surgery in 11 cases (preoperative 4; postoperative 7). In the remaining 18 cases, it was given primarily for palliation (local recurrence, 6; metastases, 12). A variety of techniques and equipment was employed during the period covered by this study. Patients in the earlier years received either 250 kvp. or 1,000 kvp. x rays. Cobalt 60, 2,000 kvp x ray or high energy electron beam (betatron 6–24 mev.) were utilized in the more recent patients. One patient was given an interstitial implant of iridium.

The average dose rate was approximately 1,000–1,500 rads per week irrespective of the type of radiation, except where the treatment target was the brain, when a lower dose rate was used. The strategy of irradiation in these cases was not uniform. The individual clinician's judgement played a prominent role in deciding on its use. In general, however, adjunctive radiation therapy was employed for unfavorable circumstances such as large lesions with borderline resectability, poor surgical margins, and when necessary amputation was refused by the patient.

RESULTS

SURVIVAL

Fifty-one of the 82 patients (62 per cent) who received curative therapy survived 5 years, while 26 of 51 patients (51 per cent) eligible for 10 year follow-up were alive (Table II). A higher survival rate was observed for patients treated by wide soft part resection. These were, of course, more favorable tumors because of clinical case selection. Nevertheless, this group did include 10 of the 11 patients who received adjunctive radiation, and 9 of them were alive at 5 years after therapy.

LOCAL RECURRENCE

The over-all rate of local recurrence after definitive therapy at our institution was 27 per cent (22/82). The development of local recurrence was most common after soft part resection for lesions which had recurred after treatment elsewhere (12 cases). Recurrence after amputation was uncommon, and occurred only in instances where a bulky and proximally situated lesion had required high amputation with questionable resection margins.

Treatment of locally recurrent disease in the absence of metastases was in most instances amputation with a view to completely eradicating disease. Six of 8 patients thus treated survived over 5 years. Local surgical excision alone or in combination with radiation was employed in 8 other cases, with no 5 year survivors. Six other patients with local recurrences received radiation therapy as sole treatment; 2 of the 6 survived over 5 years (see below).

METASTASES

Thirty-three of the 82 patients developed

TABLE II

SURVIVAL AFTER TREATMENT AT MEMORIAL SLOAN-KETTERING CANCER CENTER

	After Wide Soft Part Resection*	After Amputation†	Over-all Survival
5 years	36/50 (70%)	15/32 (47%)	51/82 (62%)
10 years	19/36 (53%)	7/15 (46%)	26/51 (51%)

* 3 patients received preoperative radiation therapy, 7 received postoperative radiation therapy.

† 1 patient received preoperative radiation therapy.

metastases (40 per cent). These occurred from 1 month to 8 years after therapy at our institution, the median interval being 18 months. Table III lists the sites of these metastases. The majority of cases presented with metastatic deposits in multiple organs and tissues, usually including one in the lung. Other patients had metastases to single sites, most commonly the lungs or pleura. All of these patients except one died of the disease. The single survivor had a breast metastasis excised 1 month after resection of a liposarcoma of the thigh and survived 10 years until death from a stroke.

PRE- AND POSTOPERATIVE RADIATION THERAPY

Eleven patients received adjunctive radiation therapy with surgery for cure (Table IV). Preoperative radiation was given in 4 cases and postoperative radiation in 7. The surgical procedures and radiation factors are recorded in the Table. Three of the 4 patients in the preoperative radiation group survived more than 5 years free of disease and 1 died of disease at 3 years. Microscopic examination of the resected tumor showed varying degrees of histopathologic changes consistent with acute radiation effects. The walls of blood vessels appeared thickened and edematous. In areas of tumor adjacent to these vessels, mild to moderate collapse of the supporting stroma and pyknosis of the tumor cells could be seen.

In the postoperative radiation group, 6 of the 7 patients survived over 5 years free of disease. One of the surviving patients was known to have had residual tumor in the extremity after an incomplete soft part resection; he was alive at 5 years without clinical evidence of disease. One patient died of tumor at 3 years.

Many of the tumors in this group of 11 patients were large or recurrent, or both. By case comparison with similar tumors in this study, amputation would have been appropriate management in many instances. Despite this, only soft part resections were done in most of these cases, and an over-all 5 year survival rate of 9/11 (82 per cent) was achieved. This suggests that the results of combined surgery and radiation therapy may be superior to the results of surgical treatment alone, even though the difference cannot be statistically substantiated.

Table III

SITES OF METASTASES

Multiple organs and tissues	15
Lung and pleura	9
Central nervous system	3
Intra-abdominal	2
Subcutaneous	2
Liver	1
Bone	1
Total	33

RADIATION THERAPY FOR LOCAL RECURRENCES AND METASTASES

Table V records 6 patients who received radiation as sole therapy for local recurrence. Five had disease situated proximally in the extremity and were not suitable candidates for treatment by amputation or disarticulation. One patient refused further surgery for a local recurrence in the leg. Marked tumor regression after irradiation was observed in 5 cases. Pain, which was the main symptom in the first case, was controlled. The patient with the leg recurrence was alive without clinical evidence of disease at 5 years. Five other patients with locally recurrent disease were treated by combined surgical resection and radiation therapy. None of these 5 patients survived 5 years.

Metastatic lesions from primary liposarcoma in an extremity were treated with radiation therapy in 12 cases (Table VI). Good subjective and objective response was noted in 9 patients (75 per cent). Radiation therapy also dramatically controlled nausea and vomiting due to brain metastases in 1 patient.

DISCUSSION

This study confirms the previously reported radiosensitivity of liposarcomas.

TABLE IV

PREOPERATIVE AND POSTOPERATIVE RADIATION THERAPY

Patient	Site of Tumor	Operation	Radiation Therapy (Tumor Dose)	Local Recurrence	Survival
Preoperative cases					
G.W.	groin	wide soft part resection	250 kvp.; 2,500 rads/3 weeks	yes	3 years, died of disease
D.M.	thigh	hip joint disarticulation	Co^{60}; 3,000 rads/3 weeks	—	5 years, alive without disease
A.M.	thigh	wide soft part resection	250 kvp.; 3,000 rads/3 weeks	—	16 years, alive without disease
P.D.	elbow	wide soft part resection	2,000 kvp.; 3,400 rads/2 weeks	yes	7 years, alive without disease
Postoperative cases					
M.W.	thigh	wide soft part resection	250 kvp.; 3,100 rads/4 weeks	—	8 years, died of unrelated cause
W.P.	thigh	wide soft part resection	1,000 kvp.; 3,600 rads/3 weeks	—	15 years, alive without disease
M.K.	thigh	wide soft part resection	1,000 kvp.; 2,600 rads/1½ weeks	—	9 years, alive without disease
L.W.	groin	wide soft part resection (known residual disease)	1,000 kvp.; 2,500 rads/2 weeks	—	5 years, alive without disease
T.K.	popliteal	wide soft part resection	10–15 mev. electrons; 3,200 rads/2 weeks	—	5 years, alive without disease
H.D.	popliteal	wide soft part resection	250 kvp.; 3,600 rads/2 weeks	yes	15 years, alive without disease
C.M.	thigh	wide soft part resection	250 kvp.; 3,600 rads/2½ weeks	yes	3 years, died of disease

With a liposarcoma arising in an extremity, radiation therapy can be used to great advantage in a variety of clinical settings and at different stages of the disease. For a potentially curable tumor, particularly one with unfavorable features such as large size, involvement of major blood vessel or nerve, a combined surgical and radiotherapeutic treatment approach should permit better control of tumor and might obviate the need for amputation. Preoperative radiation can shrink a bulky tumor mass and possibly help prevent tumor dissemination or implantation during surgery. Postoperative radiation, on the other hand, can sterilize microscopic implants or residual foci of tumor near the resection margin which may be inadequate in areas adjacent to nerve, vessel or bone. This retrospective study does not permit evaluation of the relative merits of these two methods of adjunctive radiation.

Local recurrence is common with liposarcomas and does not indicate incurability. Aggressive treatment is indicated and many of these patients with local recurrence can be salvaged. Amputation appears to be the treatment of choice in the

TABLE V

RADIATION THERAPY AS SOLE TREATMENT OF LOCAL RECURRENCE

Patient	Site of Primary Tumor	Previous Operation	Radiation Therapy for Recurrence (Tumor Dose)	Response	Survival
J.F.	axilla	forequarter amputation	1,000 kvp.; 3,700 rads/3 weeks	pain controlled, tumor regressed	15 months
S.H.	leg	wide soft part resection	(1) 10 mev. electrons; 4,600 rads/3 weeks (2) 8 mev. electrons; 3,000 rads/2 weeks	(1) tumor completely regressed, lasting 3 years (2) tumor again completely regressed	5 years, NED
M.S.	groin	wide soft part resection	2,000 kvp.; 5,700 rads/ 5½ weeks	marked tumor regression	2 years
H.R.	thigh	wide soft part resection	250 kvp.; 3,000 rads/ 2 weeks	—	8 years
N.M.	thigh	hip joint disarticulation	2,000 kvp.; 3,200 rads/ 2½ weeks	50 per cent tumor regression	8 months
M.F.	thigh	hemipelvectomy	interstitial iridium, 2.68 mg. radium equivalent	complete regression	11 months

absence of distant metastasis. In many instances, however, amputation may not be feasible because recurrent tumor involves the proximal part of an extremity with extension to the trunk. Even in these circumstances, radiation therapy alone, or with judicious surgical excision, can often control the disease.

The very frequent occurrence of metastases after curative treatment of these tumors reflects the inadequacy of our therapy. Our study indicates that radiation therapy offers excellent palliation for these patients with metastatic liposarcoma, but cure is unlikely. However, for the prevention and control of metastases, which occurred in 40 per cent of patients, a multidisciplinary approach involving surgery, radiation therapy, chemotherapy and possibly immunological manipulations, would seem to be necessary.

SUMMARY

The results of surgical and radiation therapy are analyzed in a retrospective review of liposarcomas arising in an extremity treated at Memorial Sloan-Kettering Cancer Center between 1949 and 1967.

The 5 year and 10 year survival rates were 62 per cent and 51 per cent after curative therapy; 27 per cent of patients developed local recurrences and 40 per cent developed metastases.

Adjunctive radiation therapy was employed in 11 patients, 9 of whom survived over 5 years (82 per cent). Radiation therapy produced subjective and objective responses in many cases of local recurrences and metastases, with complete regression of tumor and prolonged survival in some instances.

A combined surgical and radiotherapeutic approach to these tumors appears to offer distinct advantages, and may have obviated the need for amputation in some cases.

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TABLE VI

RADIATION THERAPY FOR METASTASES

Patient	Site of Metastases	Radiation Therapy (Tumor Dose)	Response	Survival
E.R.	(1) scalp (2) brain	1,000 kvp.; 1,500 rads/2 weeks 250 kvp.; 1,500 rads/12 days	complete regression symptoms controlled	10 months
R.K.	pleura	1,000 kvp.; 1,100 rads/1 week + Co^{60}; 1,000 rads/5 days (Total—2,200 rads)	good response	24 months
B.D.	pleura and lung	1,000 kvp.; 3,000 rads/4 weeks Co^{60}; 2,700 rads/2 weeks	good response	23 months
J.F.	pleura	1,000 kvp.; 3,300 rads/1½ weeks	good response	15 months
L.H.	1. shoulder 2. groin 3. abdomen 4. mediastinum 5. various other sites	250 kvp.; average 1,500–2,000 rads/1–2 weeks	good response	28 months
T.L.	1. opposite thigh 2. axilla	250 kvp.; 3,200 rads/2 weeks 250 kvp.; 2,000 rads/1 week	—	13 months
R.D.	liver	250 kvp.; 1,200 rads/3 days	—	—
R.M.	1. mediastinal mass 2. abdomen	excision + Co^{60}; 4,050 rads/5 weeks 250 kvp.; 1,900 rads/3 weeks	— some improvement	11 months
H.B.	mediastinum	1,000 kvp.; 4,068 rads/2 weeks	complete regression	12 months
P.M.	abdomen	1,000 kvp.; 3,200 rads/2 weeks	good response	6 months
E.D.	breast	treated elsewhere	—	4 months
R.F.	1. abdomen 2. base of skull and orbit with paresis of III, IV, VI and VII nerves	partial excision + Co^{60}; 4,100 rads/4½ weeks Co^{60}; 3,500 rads/3½ weeks	— good response	6 months

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EVALUATION OF THERAPEUTIC RESULTS IN EWING'S SARCOMA*

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MEDICAL history is replete with recordings of futile efforts to manage Ewing's sarcoma with either surgical extirpation or radiation therapy of the primary tumor as the only treatment.[1] A consistent observation throughout the world has been the infrequency with which patients remain disease-free after therapy directed solely to the primary site. The inescapable conclusion[3] with respect to therapeutic management is that one must assume "subclinical metastases are already present in patients with apparently localized tumor."

There has been increasing attention devoted to adjuvant therapy in Ewing's sarcoma during the past several years. Preliminary reports from the National Cancer Institute[4] and several other centers[2,8,11] have suggested a prolongation of the disease-free interval as well as improved survival with the application of adjuvant chemotherapy.

The present paper updates our personal experience with Ewing's sarcoma and describes the continuing evolution in the therapeutic regimen. The potential for still further improvement in the control of this previously dread disease as available modalities are more judiciously blended into an integrated approach is emphasized.

PATIENT MATERIAL AND DIAGNOSTIC EVALUATION

Sixty-six consecutive patients admitted to the National Cancer Institute since 1964 comprise the series under review. Histologic confirmation of the diagnosis has been carefully reviewed by a group of expert bone tumor pathologists as discussed elsewhere.[9] The VMA determination was negative for all cases admitted with a histologic diagnosis of Ewing's sarcoma. Pretreatment evaluation included a metastatic bone survey, chest radiographs including tomography for the majority of cases, a complete blood cell count and bone marrow biopsy, and a radioisotopic bone scan. During the past 4 years, a radioisotope brain scan and lumbar puncture have been routinely performed for evidence of central nervous system metastases.

Table I

AGE AND SEX DISTRIBUTION OF EWING'S SARCOMA

Sex	Age at Diagnosis		
	Birth–10	11–17	18–Over
Male	3	24	15
Female	9	13	3

The age and sex distributions are shown in Table I and are consistent with the usual demographic patterns of Ewing's sarcoma. The primary sites of involvement are listed in Table II. Forty-three patients had no clinical evidence of metastatic disease on

Table II

PRIMARY SITES OF INVOLVEMENT IN EWING'S SARCOMA

Site	No. of Cases	
Trunk	32	
Pelvis		26
Rib		4
Sternum		1
Scapula		1
Extremities	32	
Lower		26
Upper		6
Mandible	2	

* Presented at the Fifty-sixth Annual Meeting of the American Radium Society, Maui, Hawaii, April 21–25, 1974.
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admission. These latter patients were empirically given systemic adjuvant chemotherapy as described below and are herein referred to as the "prophylactic" series. The remaining 23 patients had recognizable metastatic disease and are referred to as the "metastatic" series.

TREATMENT METHODS

The philosophy pervading our treatment approach has been to eradicate all foci of disease, whether clinical or occult. The initial investigations with adjuvant therapy were stimulated by the awareness that few patients present with truly localized cancer, despite the clinical inability to recognize metastases. At the onset of the program, systemic chemotherapy was employed alone as adjuvant therapy[5] and later was combined with prophylactic treatment of the central nervous system (CNS).[4,6] Whereas the true incidence of CNS metastases remains uncertain in Ewing's sarcoma, we have empirically continued with whole brain irradiation (2,000 rads delivered in 2 weeks) and intrathecal amethopterin (a single dose of 10–15 mg. at the time of diagnostic lumbar puncture) because of the inability of the chemotherapeutic agents to cross the blood-brain barrier in therapeutic concentrations.

Our last description of integrated treatment for Ewing's sarcoma[4] involved chemotherapy with cyclophosphamide, vincristine, and dactinomycin as summarized in Table III. Subsequent experience noted relapse in several patients during the interval immediately following dactinomycin administration, and resumption of cyclophosphamide-vincristine promptly caused regression of the metastases. It was consequently decided to remove dactinomycin from the

TABLE III

NCI EWING'S SARCOMA ADJUVANT THERAPY PROGRAM

Protocol	Starting Date	Adjuvant Therapy*	
		Adjuvant	Dose/Schedule
S1	1964	Cyclophosphamide	Single dose (20–30 mg./kg.) or several weekly courses of 15 mg./kg. week
S2	1968	Cyclophosphamide	Four courses (40 mg./kg.) at 6 week intervals
		plus	
		Vincristine	Ten courses (0.025 mg./kg.) at 2 week intervals
S3	1969	Cyclophosphamide	Four courses (40 mg./kg.) on months 1, 2, 4, and 6
		plus	
		Vincristine	Four courses (0.04 mg./kg.) on months 1, 2, 4, and 6
		plus	
		Dactinomycin	Two courses (10–15 μg./kg. per day for 5 consecutive days) on months 3 and 5
		plus	
		CNS Prophylaxis	2,000 rads whole brain x-ray and one intrathecal dose of amethopterin (10–15 mg.)
S4	1971	CNS Prophylaxis	Same as protocol S3 *plus* four drug cycles given every 7 weeks consisting of
		Adriamycin	75 mg./m². body surface in a single dose on *day 1* of cycle
		Cyclophosphamide	Same as protocol S3 on *day 21* of the cycle
		Vincristine	Same as protocol S3 on *day 21* of the cycle

* Given in combination with irradiation of the primary site with 5,000 rads given in 5 weeks following details described in the text.

chemotherapy regimen and alternatively employ adriamycin, an antibiotic found to have marked effectiveness against Ewing's sarcoma,[7] into the adjuvant program. The S4 protocol, as outlined in Table III, was undertaken in 1971 and currently remains in use.

A further modification of treatment relates to patients with primary tumors of the ilium and/or sacrum. These cases often present with locally advanced disease and appreciable soft tissue extension of tumor. It is, therefore, not surprising that relapse of disease has been observed in the regional lymphatics or that bipedal lymphography on recent cases has demonstrated tumor involvement of the pelvic and retroperitoneal lymph nodes in some cases. In addition, 2 patients with iliac primaries developed their initial recurrence of disease at the margin of the radiation field, with tumor extending directly along the nerve roots of the lumbosacral plexus. For these reasons, patients with primary involvement of the sacroiliac bones are now treated with a radiotherapy field encompassing the lumbosacral plexus and the retroperitoneal lymph nodes up to the top of the second lumbar vertebra.

We have persisted with the use of a 5,000 rads tumor dose to the primary site delivered over 5 weeks in fractions of 200 rads, irrespective of tumor bulk. This dose is somewhat lower than advocated by others but appears adequate, at least in combination with the chemotherapy as given (in part) concurrently. Only 2 patients have developed clinical evidence of local recurrence after this dose as could be appreciated premortem and a third case had microscopic evidence of persistent local tumor at autopsy in addition to generalized metastatic disease. It is our opinion that this reasonably low incidence of local recurrence after 5,000 rads does not justify the consistently exaggerated fibrosis and resultant disability which accompanies higher radiation doses. Furthermore, the importance of shielding a strip of skin and subcutaneous tissue when irradiating an extremity must be appreciated. Whenever feasible, the latter will serve to significantly reduce the severity of soft tissue fibrosis while maintaining an avenue for lymphatic drainage from the distal portion of the limb.

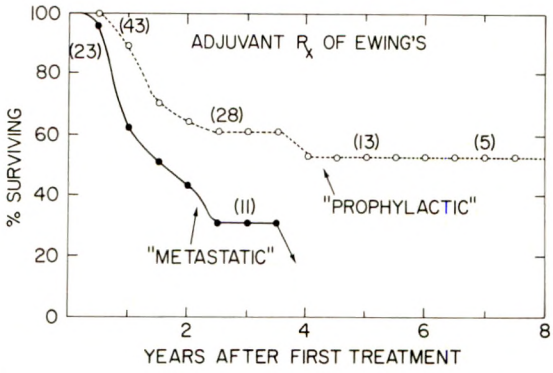

FIG. 1. Actuarially calculated survival curves for the "prophylactic" and "metastatic" groups of Ewing's sarcoma patients in the NCI series. Number of patients at risk for various time intervals is shown in parentheses. There are no deaths from intercurrent disease.

RESULTS

Uncorrected survival rates for the entire series are shown in Figure 1. The patients with detectable metastases upon admission have a median survival time of 18 months and 1, 2, and 3 year survival rates of 62, 44, and 31 per cent, respectively. The patients in the "prophylactic" adjuvant therapy group have a 5 year survival rate of 53 per cent and the corresponding continuously-free-of-disease rate is 42 per cent. The clinical features and determinants which influence or correlate with these survival rates are detailed in a companion paper[10] and will not be reiterated here.

Comment is warranted on the fact that maintenance therapy has not been given except for those patients having unremitting metastatic disease. Disease-free survival in the "prophylactic" series thus represents survival without any therapy following completion of the initial 6 month program. It may also be noted that intrinsic central nervous system involvement

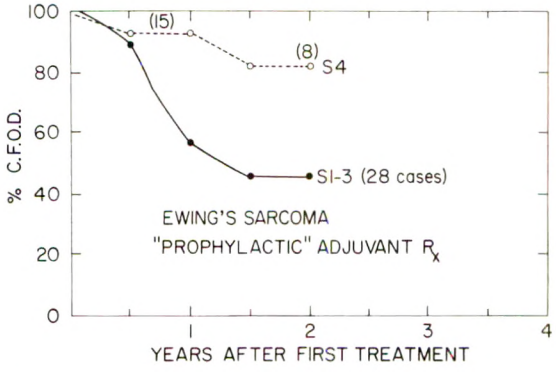

FIG. 2. Actuarially calculated survival continuously free of disease for the current S_4 protocol is compared to the S1–3 protocols (combined). The number of patients at risk for various time intervals is shown in parentheses. All 28 cases in the S1–3 protocols have been followed for more than 2 years since initial treatment.

by tumor has not been observed in the last 44 patients treated with CNS prophylaxis since 1969.

Both over-all survival and disease-free survival have shown further improvement since initiation of the S_4 protocol. Figure 2 compares the survival continuously-free-of-disease for the S_4 series with the earlier adjuvant protocol cases. The obvious prolongation of the disease-free interval in the S_4 series is becoming reflected in over-all survival, none of the 15 patients accessioned into the "prophylactic" group during the past 30 months having expired to date.

DISCUSSION

Presently available chemotherapeutic agents have far greater effectiveness against small tumor cell populations as compared to tumor masses of considerable bulk. While adjuvant chemotherapy can have a beneficial role in the presence of macroscopically advanced disease, the greatest potential clearly lies in the use of adjuvant therapy where microscopic foci of metastatic spread are the only residual disease. The results of the present study are consistent with these principles. The 2 year survival rate of 44 per cent for patients with detectable metastases bears witness to the merit of adjuvant therapy and even compares favorably with the usual historical experience for localized disease.[1] However, few patients presenting with metastases experience long term, disease-free survival in the absence of maintenance chemotherapy. Thus, while a substantial increase in survival can be achieved, the goal of tumor eradication has yet to be achieved with any frequency in these cases.

The situation is more encouraging for patients without clinical evidence of metastases, as might be anticipated. These patients, while admittedly seldom free of occult dissemination, have a smaller tumor burden and are more amenable to eradication of metastatic disease with adjuvant therapy. Disease-free survival following termination of all therapy is being increasingly prolonged (Fig. 2) and long term survival (usually without relapse) has been observed in approximately one-half of patients. Recurrence on a local or regional basis is now a seldomly observed event. Relapse is rather the consequence of uncontrolled dissemination, and the need for further refinement of the current adjuvant program is apparent. Continued progress will be markedly facilitated by the referral of patients with Ewing's sarcoma to those centers where a dedicated effort is being made to develop improved therapeutic methods.

SUMMARY

The philosophy pervading our treatment approach to Ewing's sarcoma has been to have therapy encompass all foci of disease, including sites of occult or potential involvement in addition to obvious clinical manifestations.

The experience with integrated methods of treatment in 66 consecutive patients at the National Cancer Institute is reviewed. A median survival of 18 months (44 per cent 2 year survival rate) for patients with recognizable metastases on admission bears impressive witness to the value of adjuvant therapy in Ewing's sarcoma.

Even more encouraging, an uncorrected

5 year survival rate of 53 per cent (42 per cent continuously free of disease) for patients given "prophylactic" adjuvant therapy indicates the potential for permanent control of disease in a significant fraction of cases with clinically localized primary tumors.

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CHILDHOOD RHABDOMYOSARCOMA*

ANALYSIS OF COORDINATED THERAPY AND RESULTS

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RHABDOMYOSARCOMA, a malignant tumor arising from striated muscle, is the most common soft tissue sarcoma that develops in children. It has been described as a tumor which invades locally, extending along fascial planes for great distances. These extensions account for the high incidence of local recurrences after surgery alone (50 to 60 per cent).[20] The tumor also metastasizes frequently (21 per cent, Horn *et al.*,[7] 52 per cent, Lindberg[14]), both by the blood-stream and lymphatic channels.

Two year survival figures in children with rhabdomyosarcoma of the head and neck have been published from this institution.[4] The present report includes a 3 year follow-up on the head and neck rhabdomyosarcoma cases and a review of the cases with other primary presentations treated at The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, from 1950 to October 1970. The data from 78 of these children were analyzed in 1966.[22]

It has been our intention to compare the outcome in the cases that received coordinated treatment (surgery, radiation therapy, and planned intensive multidrug chemotherapy) with the outcome in those that were not managed by preplanned coordination among the different modalities. In this paper, radiotherapeutic considerations have been emphasized.

CLINICAL MATERIAL

A total of 113 children between 4 months and 15 years of age with a diagnosis of rhabdomyosarcoma has been included. The diagnosis of tumor type was based on the pathologic classification used at M. D. Anderson Hospital: (1) pleomorphic, (2) alveolar, and (3) embryonal; with sarcoma botryoides considered as a subdivision of the third group. The histologic descriptions are well known.[1] The pleomorphic variety usually occurs in adults, the alveolar variety in the adolescent, and the embryonal variety in children.[7] Patients with sarcoma botryoides have not been included in this analysis.

The age and sex of patients are seen in Figure 1. Primary site as related to histology is shown in Table I. The most common initial site for the development of this tumor was the head and neck area (60 per cent), especially the orbit, maxillary antrum, and nasopharynx. The tumor next most commonly arose in the genitourinary tissues (15 per cent), particularly in the bladder, the prostate, and the peritesticular tissues. Other sites of origin include the extremities (14 per cent), the body wall (6 per cent), and the retroperitoneum (5 per cent). A detailed breakdown of the specific areas of primary involvement is given in Table II.

In the evaluation of the outcome of treatment (*i.e.*, survival and/or duration of disease control), data from only 93 of the 113 children were used. Twelve children received primary treatment outside the M. D. Anderson Hospital and 8 others had fol-

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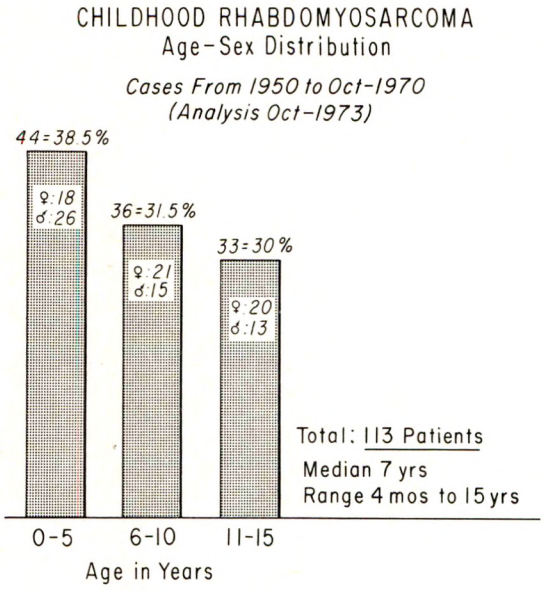

FIG. 1. Distribution of cases.

low-up periods of less than 3 years. These 20 cases were omitted from analysis of 3 year end results.

TREATMENT

Since 1964, the policy consisted of the application of all possible types of treatment. The sequence was dependent upon the location and extent of the tumor and included surgical removal, when possible, radiation therapy and intensive chemotherapy (VAC: Vincristine+Actinomycin-D +Cyclophosphamide). Prior to 1964 the children received surgery only, surgery and radiotherapy or single drug therapy or chemotherapy combinations other than VAC.

SURGERY

The type of surgery employed has varied from a simple biopsy in the head and neck area to pelvic exenteration in embryonal rhabdomyosarcoma of urogenital system.

RADIOTHERAPY

Radiotherapy techniques have been adapted to each individual case. Equipment used was cobalt 60, electron beam, or photon beam, depending on the site to be treated and the depth needed. Usually a tumor dose of 5,000 rads delivered in 5 weeks plus an additional 500 to 1,000 rads in 2 days or 5 days through reduced fields have been given. At times, a split course of therapy was necessary.

Orbital lesions were treated using anterior and lateral wedge-filtered fields. The lateral field was angled posteriorly to avoid the contralateral eye and 60° wedges were used to compensate for this angulation.

The radiotherapy techniques used for lesions of the upper air passages consisted usually of parallel-opposed Co^{60} fields or a combination of wedged-filtered fields when sinuses were involved (Fig. 2; and 3).

Rhabdomyosarcomas arising in the soft tissues, *i.e.*, cheek or temple, were treated with an appositional electron beam field. Lesions arising in the neck were irradiated with an anterior Co^{60} field with the head in an extended position. This field was opposed with a posterior field to deliver a more uniform dose. Thus the cervical and supraclavicular lymph node-bearing areas were easily covered, while the larynx and

TABLE I

SITE OF PRIMARY—HISTOLOGY

Site	Embryonal		Alveolar		Other	Number	Per Cent
Head and neck	43	79%	10	18%	—	53	47
Orbit (eyelid)	15	93%	1	6%	—	16	14
Genito-urinary area (small)	14	82%	2	11%	1	17	15
Extremities	5	31%	11	69%	—	16	14
Retroperitoneal area	3	—	—	—	3	6	5
Trunk	2	—	1	—	2	5	4
Total	82		25		6	113	

TABLE II

MAJOR PRIMARY LOCATION OF 113 LESIONS

Head and Neck (69 Cases)		Genitourinary Area (17 Cases)		Extremities (16 Cases)		Trunk (11 Cases)	
Orbit	16	Bladder	5	Thigh	7	Upper torso	4
Maxillary antrum	10	Testis	2	Leg	4	Lumbar	2
Nasopharynx	8	Scrotum	3	Arm	3	Retroperitoneal	5
Cheek (masseter m.)	7	Spermatic cord	2	Foot	2		
Scalp (temporal m.)	6	Epididymus	1				
Neck (ECM)	5	Urogenic ridge	1				
Middle ear	4	Broad ligament	1				
Palate	3	Penis	1				
Nasal cavity	2	Pelvis	1				
Tonsillar area	2	(nonspecific)					
Gum	2						
Ethmoid	1						
Pterygoid fossa	1						
Pharyngeal wall	1						
Larynx	1						

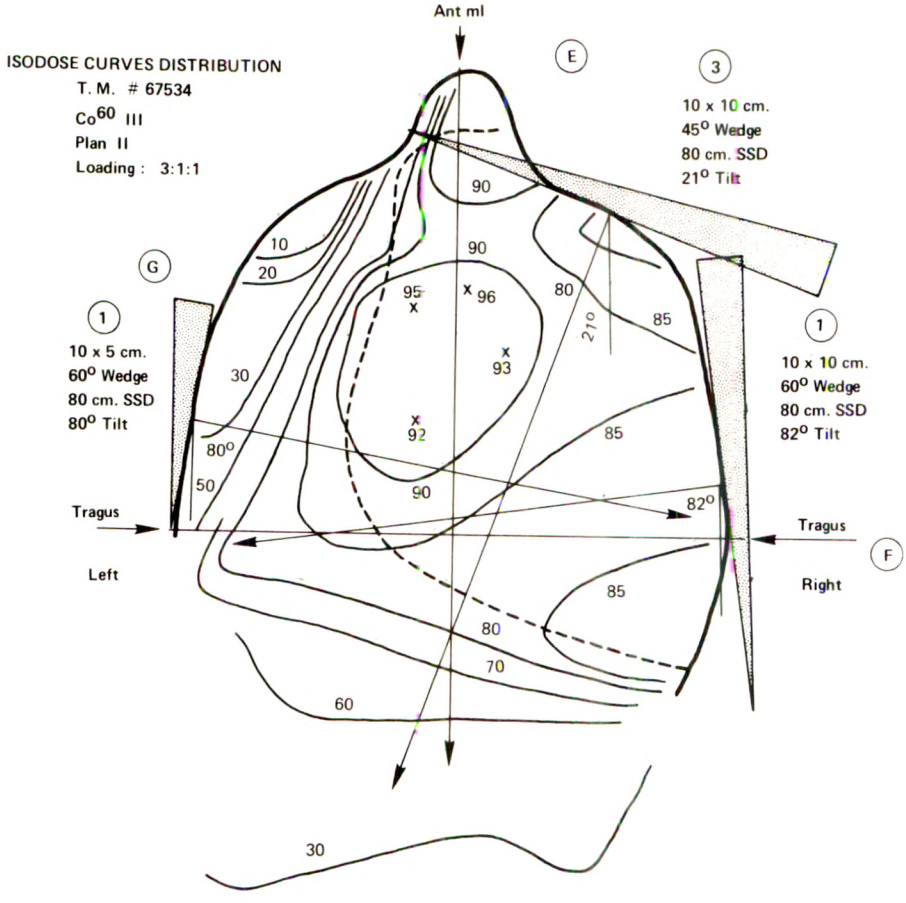

FIG. 2. Isodose curves distribution. Eight year old girl with rhabdomyosarcoma in the nasopharynx, with involvement of right ethmoid and sphenoid sinus. Patient received 5,500 rads in $5\frac{1}{2}$ weeks and complete course of VAC. She is alive at 5 years.

spinal cord were avoided.

Because of the incidence of cervical node metastasis (35 per cent at initial examination and an additional 9 per cent during or after original treatment), the homolateral cervical lymph nodes were irradiated in all cases of head and neck rhabdomyosarcomas except for primaries arising in the orbit, paranasal sinuses, and nasal cavity, as the incidence of cervical node metastasis from these sites is low. The neck received 5,000 rads given dose in 5 weeks through a single anterior field.

Middle ear tumors were treated with a combination of open and 45° wedged-filtered fields with equal or 2:1 loading with Co^{60}; the total dose to base of skull and petrous pyramid was 5,500 rads in 5.5 weeks or 6,000 rads/6 weeks or a split course, usually given after local excision or biopsy.

Protective devices in head and neck treatment such as stents (intraoral), lead blocks, lead cylinders (eyes), and corks were employed to protect sensitive organs or mucous membranes.

For other areas, the techniques varied. Usually the fields were devised as simply as possible, avoiding the irradiation of normal structures. Dose-rate schedules and total tumor dose were modified to 850 rads in 1 week and even 750 rads in 1 week when large volumes were treated, doses being as high as 3,000 rads to entire abdomen and 4,500 to 5,000 rads to pelvic area. Adjustments of dose were made depending on the patient's age and tumor location.

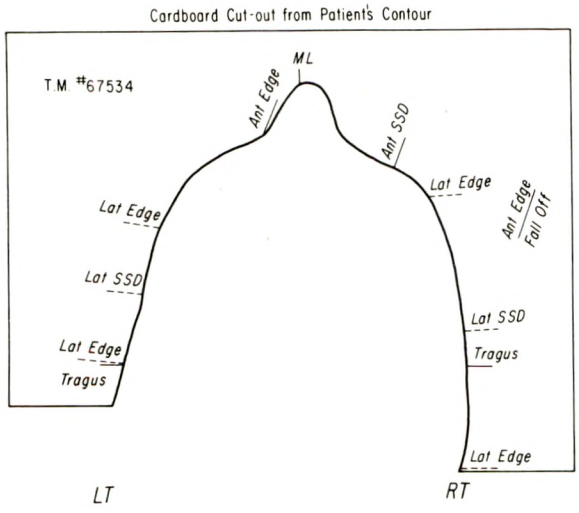

Fig. 3. Cardboard cut-out from patient's face contour, used to position the previous wedged-filtered fields (Fig. 2).

In summary, there was no standard radiotherapy technique for rhabdomyosarcoma. The planning and actual therapy required multiple machinery, gadgetry, and sophisticated dosimetric calculations.

CHEMOTHERAPY

Since 1964, two chemotherapy regimens were used, each based on combined treatment with Vincristine, Actinomycin-D, and Cyclophosphamide.[21] In the original VAC schedule, Vincristine was given weekly in the dose of 2 mg./m.^{2} (maximum single dose, 2 mg.) intravenously for 12 doses. The initial dose was given as soon as the postoperative status stabilized. If excessive toxicity occurred, an effort was made to complete at least 8 doses. Actinomycin-D was given in divided daily injections over a period of 5 to 7 days in the cumulative total dose per course of 75 μg./kg. Subsequent courses of Actinomycin-D were given every 3 months for a total of 5 courses. Cyclophosphamide was started after completion of radiotherapy and stabilization of blood cell counts. The dose was 2.5 mg./kg. and was given orally. This drug was administered daily for 2 years. Chemotherapy was discontinued after 2 years if there was no evidence of disease activity.

Some patients were treated on the intermittent and intensive pulse schedule.[6] On such a schedule, Actinomycin-D was administered at 3 month intervals as described above. Cyclophosphamide pulses were given every 6 weeks. Each pulse consisted of 7 days (or less if leukopenia below 1,500 WBC/mm.^{3} occurred) of Cyclophosphamide in the dose of 10 mg./kg. intravenously or postoperatively. Vincristine was given in the dose of 2 mg./m^2. (maximum 2 mg.) on days 1 and 8 of each Cyclo-

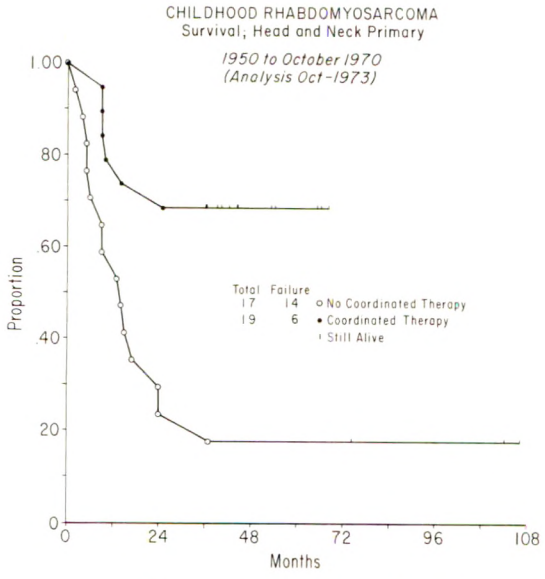

FIG. 4. Actuarial comparison of survival curves of patients receiving coordinated therapy and no coordinated therapy. Each upright line represents a living case.

phosphamide pulse. The treatment was continued for 2 years.

RESULTS

Head and Neck (Excluding Orbital Lesions)

Recently Donalson *et al.*[4] analyzed the data on 25 children with rhabdomyosarcoma in head and neck treated with coordinated radiotherapy and chemotherapy at this institution. They reported that 14 of 19 children (74 per cent) were alive without disease at 2 years. The follow-up study of these patients has demonstrated a 3 year survival figure of 68 per cent and local control rate of 89 per cent. Thirteen patients of the 19 are surviving from 36 months to 85 months. All have been off chemotherapy 12 months or more. Five have passed the 5 year point. In our previous experience, the survival rate was 18 per cent at 3 years when the primary tumor was located in superficial tissues of the head and neck. When the primary lesion was in the nasopharynx or maxillary antrum or tonsillar area, the survival was poor (0/6).[14,21]

Figure 4 is an actuarial comparison of survival curves of the present and past experiences. Survival among those receiving the current therapy program was significantly better ($p=0.01$) than survival among those treated earlier. We have now 8 additional patients in the coordinated radiotherapy-chemotherapy program and 6 of the 8 are alive and free of disease 13 to 27 months after start of therapy. Figure 5 is the comparison of local recurrence of the 2 groups with p value of 0.01 that is significant.

Orbital Lesions (16 Cases)

Among the 16 orbital lesions, the primary tumor was located in the eyelids in 3. Of 16 patients with localized disease, 81 per cent show no evidence of disease at 3 years. Usually, enucleation and radiotherapy have been used. Five year and 10 year survival figures were both 74 per cent (Fig. 6).

Genitourinary Lesions (17 Cases)

The most common site for the primary lesion was bladder (5/17). The other sites for the primary tumor were scrotum in 3, testis in 2, spermatic cord in 2, epididymis

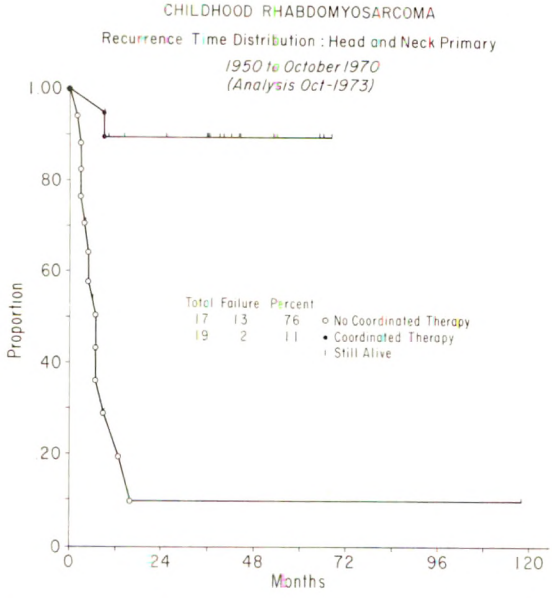

FIG. 5. Actuarial comparison of recurrences occurring in patients receiving coordinated therapy and no coordinated therapy. Each upright line represents a case with no recurrence.

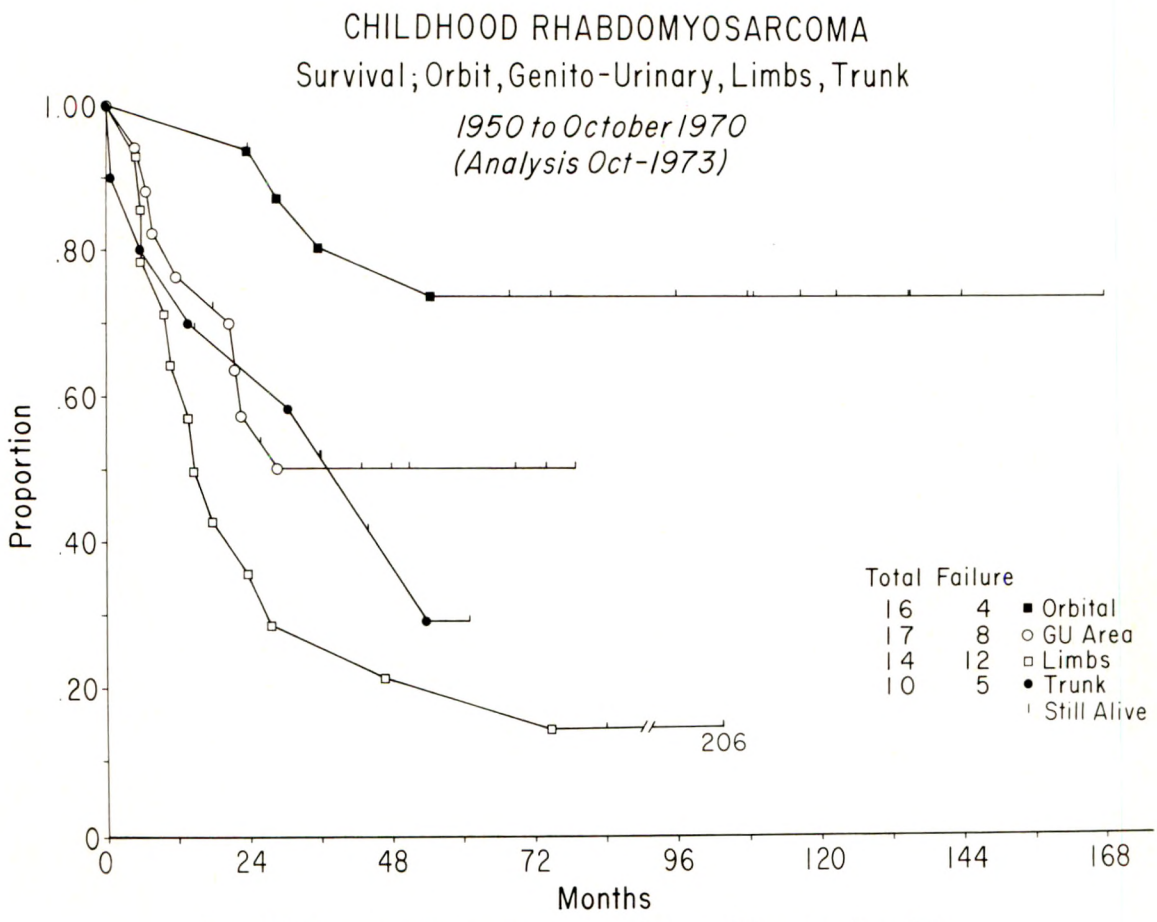

Fig. 6. Each upright line represents a patient surviving at a given time.

in 1, urogenital ridge in 1, broad ligament in 1, indeterminate place in pelvis in 1 and penis in 1. Seven out of 17 who had localized disease show no evidence of disease at 3 years (Fig. 6). The treatment of these 7 patients is given below.

Of the 3 with primary tumor in the scrotum, 2 had local resection alone and 1 had Vincristine, local resection and radiotherapy.

One patient with the primary lesion in the bladder received preoperative radiation and Vincristine, then surgery followed by Vincristine alone.

One patient with a testicular primary tumor had Vincristine, Actinomycin-D, and Cyclophosphamide after needle biopsy, surgery, and radiotherapy.

One patient whose primary lesion involved the spermatic cord had surgery, preoperative VAC chemotherapy and radiotherapy postoperatively.

One patient with the primary tumor in the broad ligament had surgery (total abdominal hysterectomy plus bilateral salpingo-oophorectomy), radiotherapy, and VAC.

Extremities (16 Cases)

Approximately one-third of the children with rhabdomyosarcoma primary in the extremities (31 per cent) had metastases on admission. The most frequent primary sites were the thigh (6/16) and leg (5/16). Thus the lower extremity tumors constituted 69 per cent (11/16) of the total. Three patients received coordinated therapy but failed. Sixty-nine per cent of cases were alveolar rhabdomyosarcoma. The over-all 3 year survival rate was 28 per cent (Fig. 6). Of

the 4 patients surviving more than 3 years, 2 are still alive. One had forequarter amputation 17 years ago for the tumor in the arm. The other had a primary tumor in the left thigh and had local excision and intra-arterial infusion with Actinomycin-D and Phenylalanine mustard. Of the other 2 patients, 1 died at 47 months and 1 at 75 months.

Trunk (10 Cases)

Of the 10 cases treated here (Fig. 6), 5 have survived 3 years or more, 2 of whom had primary tumor arising from the upper torso with metastasis on admission One of 5 has survived 54 months, including the $2\frac{1}{2}$ years after his lung metastases were irradiated and resected. The second is alive with NED at 36 months. Two other children with lesions in the lumbar area and paraspinal muscles were treated with radical resection, radiotherapy and complete VAC and are alive with NED at 44 and 36 months. The fifth child, a 6 year old girl, had a large retroperitoneal embryonal rhabdomyosarcoma attached to bladder and right hypogastric vessels and had metastases to skull, pubis, and thoracic vertebra (with collapse). She was treated with partial resection, complete VAC chemotherapy, and palliative radiotherapy to spine and has NED at 5 years 1 month.

ANALYSIS OF LOCAL FAILURES AND DISTANT METASTASIS

The duration of local control to the time of first local recurrence was 8 months; 94 per cent of the local failures occurred in the first year, and all occurred within 2 years of the diagnosis. The incidence of local failure was more frequent in the group where no VAC was given, 76 per cent against 11 per cent in the head and neck cases that received coordinated treatment (Fig. 5). When patients were seen on admission with recurrent lesions, none were salvaged. However, in the cases where recurrence developed while under observation in our institution, 38 per cent were salvaged by second treatment.

Distant Metastases

The mean time for appearance of first metastasis was 9 months after starting treatment; 74 per cent occurred in the first year of therapy and all of them within 2 years of diagnosis. The mean time between metastasis and death was 7 months.

No child was salvaged when a metastatic lesion was present, with the exception of one embryonal rhabdomyosarcoma of retroperitoneal area metastatic to bone (treated by partial surgery and complete VAC and palliative radiation to bones).

Tumor extension was the cause of death in all of the cases except one (intercurrent disease with malignant hypertension and nephrosclerosis).

Necropsy Findings

Autopsies were performed in 25 of these children. In 4 (16 per cent) of the 25 cases, local recurrence was assumed to be direct cause of death. Distant metastatic disease was the cause of death in 11 patients (44 per cent), and both recurrence and metastases were implicated in 10 patients (40 per cent).

The organs where metastases occurred most frequently were: lungs (80 per cent), bones (64 per cent), serous membranes (60 per cent). Cardiac and pericardial involvement was found in 20 per cent at autopsies. Liver metastases were less frequent. Three epidural space metastases were diagnosed premortem. In most of the instances *multiple organs* were involved.

Total Lung Irradiation for Metastases

Nine children who developed pulmonary metastases were irradiated with Co^{60}, 1,500 rads in 2 weeks plus a boost with reduced field of 2,000 rads, or 2,000 rads in 3 weeks plus 1,000 rads in 1 week boost or with 250 kv., 3.0 mm. HVL Cu 2,400 in 23 days or 1,500 rads in 3 weeks. Total clinical disappearance of metastatic lesions was observed in 2 out of 9, partial response in 1 of 9 and no response in 6 of 9. All patients died

with disease in lungs, 5 confirmed by necropsy (the remaining confirmed by chest roentgenograms). Response was temporary, the children being radiologically "free of disease" for only about 2 months. In 2 cases, however, the survival with lung metastases was $2\frac{1}{2}$ years; 1 on admission had alveolar rhabdomyosarcoma in scapular area metastatic to cheek. He was treated with surgery and Actinomycin-D. Later he developed lung metastases which were irradiated with 250 kv., 1,500 rads in 3 weeks and subsequently resected. The other had retroperitoneal tumor and was admitted with paraplegia because of block at level of L4. Lung metastases were treated outside with a 5,000 rads tumor dose, and the patient was treated here with VAC chemotherapy. Response was incomplete but he survived 2 years 7 months with lung disease.

COMPLICATIONS

RADIOTHERAPY

Head and Neck

Eye: Eye complications developed in 29 per cent during or after radiation treatment of lesions of the orbit, ethmoid, nasopharynx, and maxillary antrum when the eyes were included in the fields. The most common developments were chronic conjunctivitis, keratitis, and uveitis 3 months to 3 years after the end of therapy. Two children required enucleation because of sympathetic ophthalmia.

Cataracts developed in almost all of the patients in whom the eye was included in the treatment field. Vision was saved by cataract extraction.

Face: Temporomandibular fibroses were observed when more than 6,000 rads were delivered to the midline. Other delayed complications were observed: radiation necrosis (2 cases), dental decay (2 cases) and impaired growth of the irradiated bones (2 cases, 5 years, and 7 years after treatment to orbit and nasopharynx). The complications were more significant in the younger patients.

Abdomen-Pelvis

Complications in the area included pelvic fibrosis (1 case), radiation hepatitis (1 case), shortness of femur (1 case), and atrophy of penis (1 case). No severe gastrointestinal disturbances were observed.

Extremities

Lymphedema (forearm and foot), lymphedema of the leg (1 year after radiation, 1 case) and frozen shoulder (treated with disarticulation) were seen.

We have not considered as a complication the reactions (sometimes severe) that the patients manifest during the coordinated therapy, *i.e.*, mucositis, diarrhea, nausea, and vomiting. The most severe reactions were observed when the head and neck areas were treated by coordinated therapy; most of the patients needed hospitalization and supportive measures.

CHEMOTHERAPY

The most severe reactions were noted when the Actinomycin-D course overlapped radiation therapy in the head and neck cases. Severe mucositis was common and morbidity was protracted. Blood cell count depression, particularly thrombocytopenia, was regularly noted in these patients. Occasional instances of thrombocytopenia occurred also following Actinomycin-D courses which did not coincide with radiotherapy.

Leukopenia generally followed the pulse course of Cyclophosphamide but was rarely seen when the drug was given on the daily schedule. Chemical cystitis with hematuria and urinary complaints were recorded in 14 of 58 patients (Cyclophosphamide was discontinued in 11).

DISCUSSION

Rhabdomyosarcoma in children has been studied in *great* detail during this last decade.[10–13,15,17] The concept of "incurability" of this disease is changing dramatically. Until recently, therapy generally was radical surgery, which invariably resulted

in large functional and cosmetic defects particularly in the head and neck area. With the addition of irradiation, the local control of the disease had improved,[2,16,18] but patients still succumbed to distant metastases. Today, the survival rate has been increased considerably with the use of combined modal approach[5,9] that includes the intensive use of multidrug chemotherapy.

Analysis of our data indicates that coordinated therapy has been extremely beneficial in the children with primary tumor involving head and neck sites other than orbit. Many children with lesions arising in nasopharynx, maxillary antrum, and faucial arch, can now be saved with this regimen.

For patients with primary tumors arising in sites other than the head and neck area, it has not been possible, because of the small numbers of patients, to evaluate the influence of the coordinated approach on survival rates. The curves derived from these data (Fig. 6) included all cases and were presented merely to indicate some variation in prognosis dependent on the site of the primary tumor.

The responsiveness of rhabdomyosarcoma to combined modality treatment, as shown here, suggests the provocative possibility that the extent of radical surgery formerly considered necessary in many cases could be avoided. There is a movement to critically re-evaluate, for example, the need for radical amputations and exenterations.[3,19]

The chemotherapy program was based on several considerations. Each of the three drugs used singly had some antitumor effect on the tumor. It was the expectation that the antitumor effects, when the drugs were used in combination, would be at least additive. The drugs had different mechanisms of action and, with the exception of marrow depression by both Actinomycin-D and Cyclophosphamide, different types of major toxicity. Thus, schedules using the drugs in combination could be applied clinically. Moreover, Actinomycin-D reportedly has a synergistic action with irradiation, thus enhancing the therapeutic potential of irradiation.

The greatest clinical value of adjuvant chemotherapy probably comes from its effect on micrometastases. Both surgery and irradiation are target-limited modes of treatment and thus are ineffective against tumor cells located outside the target zones. Systemic chemotherapy, conversely, does reach distant foci of tumor and, as shown in animal studies, is particularly effective when the tumor cell population is small. Chemotherapy is locally effective also and will reduce the tumor bulk that must be eradicated by surgery and/or irradiation. Conversely, chemotherapy will exert antitumor effect against postsurgical and postirradiation residual tumor cells as well.

SUMMARY

The current utilization of an intensive coordinated therapy program (surgery, radiotherapy, and intensive multidrug chemotherapy) has increased the success rate in treatment for rhabdomyosarcoma in children. A 68 per cent 3 year survival and 89 per cent local control of rhabdomyosarcoma of head and neck substantiate this.

These results suggest that surgical procedures regarding rhabdomyosarcoma primary in other sites require re-evaluation and possible modification.

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PROGNOSTIC FACTORS FOR SURVIVAL IN EWING'S SARCOMA*

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WITH the use of adjuvant chemotherapy, the survival in Ewing's sarcoma is being improved.[4–6,8,9] With increasing interest, as demonstrated by the development of randomized, prospective studies by the cooperative chemotherapy groups, it becomes increasingly important to evaluate the disease parameters which may affect survival.

Analysis of survival patterns in 66 consecutive patients treated at the National Cancer Institute has provided information on a number of variables which appear important in analyzing results in sequential comparisons and may be of aid in deriving stratification procedures in randomized studies. Recognizing that different chemotherapeutic regimens may evidence differences in many of the parameters to be described, it becomes important to carefully document and evaluate all pertinent observations for continuing and retrospective comparisons.

SEX AND AGE

The preponderance of males in the incidence of Ewing's sarcoma has been universally reported and accepted.[1–3,10] The close relationship of age and sex distribution has not been widely appreciated. Glass and Fraumeni[3] have reported on the earlier median for peak incidence of osteosarcoma, and to a lesser degree of Ewing's sarcoma in the female. This has been demonstrated in this series (Fig. 1) and a distinct difference in survival with age has been noted (Fig. 2; 3; 4; and Table II). By adding 4 years to the age of the female, the male-female ratio is evened out over the age spectrum and the age-specific sex difference disappears. Whether this is a legitimate means

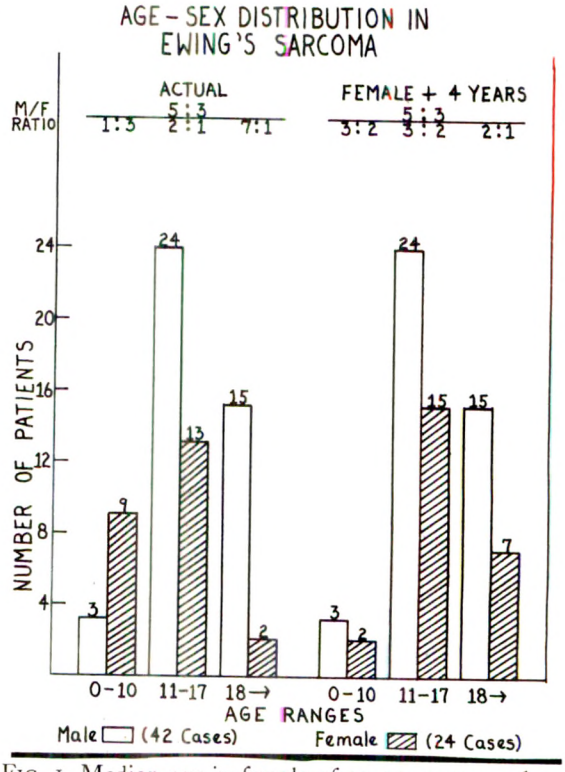

FIG. 1. Median age in female of 11–12 years can be adjusted to that of male of 15–16 years by adding 4 years, thereby equalizing age distribution and sex dependent survival variance (See Table II).

to reduce the complexity of stratification procedures remains to be determined. In favor of this procedure is the association of peak tumor incidence with the physiological growth spurt in both males and females. The earlier median incidence of 11–12 years for the female compared with 15–16 years for the male correlates with that reported by Glass and Fraumeni[3] and also with the earlier onset of puberty and the adolescent growth spurt in the female.

Another provocative finding in relation to this physiologic growth spurt has been

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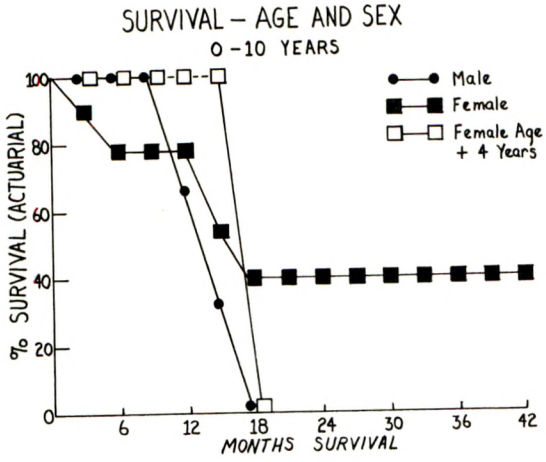


FIG. 2. 0–10 year age group. Effect of adding 4 years to female age.

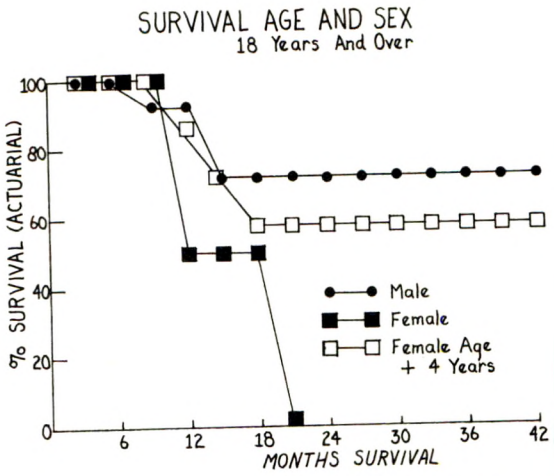


FIG. 4. 18 and over age group. Effect of adding 4 years to female age. Male-female survival not significantly different.

the appearance of relapse coincident with the onset of menses in three instances (one at 44 months; one at 24 months; and one at 21 months after initiation of therapy). All 3 patients had received intensive chemotherapy for a period of 6 months only. The use of more prolonged chemotherapy in pre-pubertal females may be a worthwhile consideration.

TUMOR SITE

Several studies have shown the correlation of the primary tumor site with survival.[2,6,7,8,10] In this study, the improved survival for the peripheral locations (below the knee and elbow and the mandible) as contrasted with trunk locations is further emphasized by the intermediate survival rates for the femur and humerus (Table 1; Fig. 5).

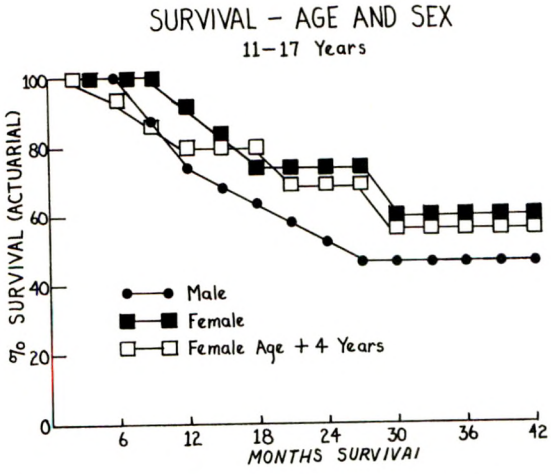


FIG. 3. 11–17 year age group. Negligible effect of adding 4 years to female age. Male-female survival not significantly different.

SYSTEMIC SYMPTOMS

These include weight loss, otherwise unexplained anemia and most importantly fever (Fig. 6). The presence of fever or other systemic symptoms does not necessarily indicate a hopeless situation in the individual case as has been accepted in the past.[1,10] In the presence of documented

TABLE I

SURVIVAL—SITE IN EWING'S SARCOMA*

Site		Survival (2 Years)		
Trunk	32	7/23		30%
Pelvis	26		7/19	
Ribs, sternum, scapula	6		0/4	
Central Long Bone	16	4/9		44%
Femur	13		3/6	
Humerus	3		1/3	
Peripheral Long Bones	18	11/12		92%
Below knee	13		8/8	
Below elbow	3		1/2	
Mandible	2		2/2	

* NCI Total cases—66 At risk 2 years—44

TABLE II

SURVIVAL—AGE IN EWING'S SARCOMA*

	Total Male and Female	Total Male and Female+4
0–10 Years	30%	0
11–17 Years	51%	51%
Over 18 Years	70%	67%

* NCI Cases at risk 3 years—35.

fever, 20 per cent of patients in this series have survived more than 3 years.

LACTIC DEHYDROGENASE

The apparent value of this determination was discovered on retrospective analysis because of a change in reporting the unit values from a maximum level of 680 units to 340 units. At present, a sharp break in survival occurs (Fig. 7) at a recalculated level of 170 units (half of the normal maximum). Determination of the source of the LDH by measuring iso-enzymes may help separate those cases with elevation secondary to surgical procedures and/or anesthesia from those related to total tumor volume.

The combination of initial LDH levels with systemic symptoms provides a very distinct prognostic indicator for survival (Fig. 8). Since the coincidence of the two findings is only 70 per cent, it is evident that the two findings are not completely interdependent.

WHITE BLOOD CELLS

The total white blood cell count when elevated above 7,000 per cu. mm. indicates a poorer prognosis (Fig. 9). Also a total lymphocyte count above 2,000 per cu. mm. indicates a significantly poorer survival, particularly in those patients presenting with no clinical metastasis (Fig. 10). The current interest in immune mechanisms

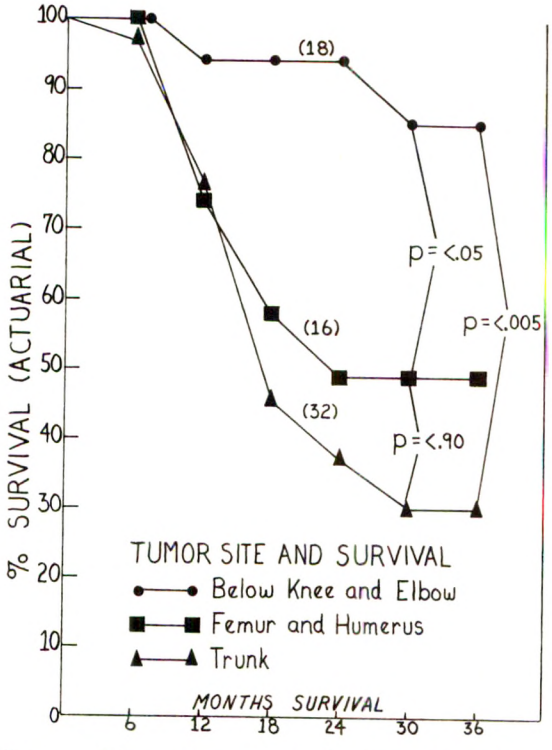


FIG. 5. Site and survival. Median survivals in months are respectively 17.4, 20.7, and >60 for trunk, humerus and femur, and peripheral bones, including the mandible.

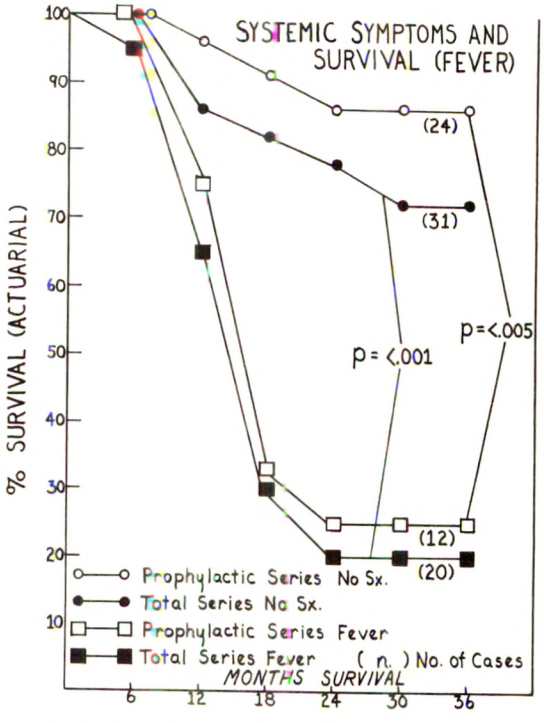
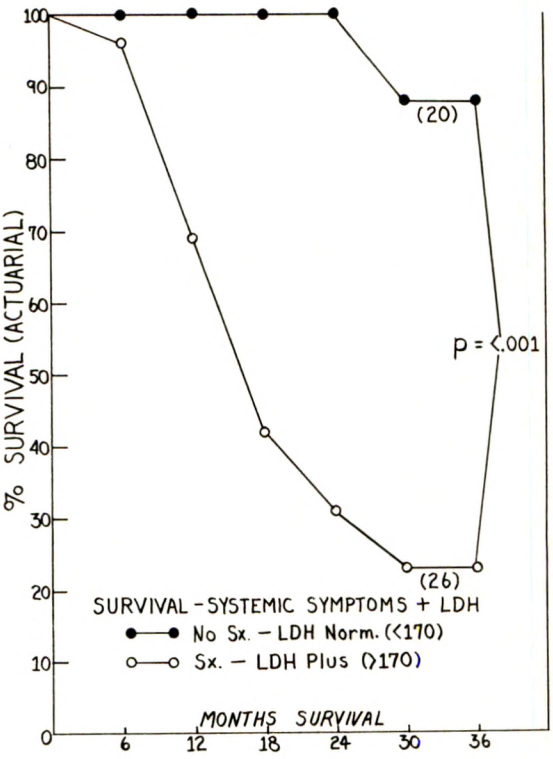


FIG. 6. Effect of fever on survival. Median survival with fever 16 months, with no symptoms >60 months.

FIG. 8. Combining LDH and systemic symptoms provides effective prognostic indicator. Overlap is 70 per cent for systemic symptoms and LDH >170.



and the methods of evaluating immune competence may aid in elucidating the meaning and significance of this unexpected relationship.

ERYTHROCYTE SEDIMENTATION RATE

This procedure would be anticipated to parallel fever and LDH as an indicator of tumor volume. Further time and/or more cases will be required to determine its significance and any useful role in the development of randomized studies. Retrospective comparisons may be sufficient to ensure balance in randomized studies rather than further complicating preliminary stratification procedures.

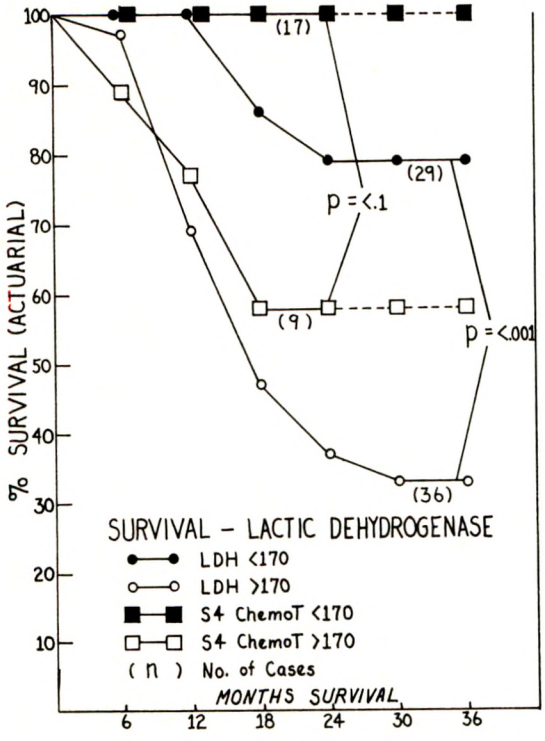


FIG. 7. Relationship of lactic dehydrogenase levels to survival. Arbitrary division at 170 units provided highly significant difference for total series. Median survivals 17.4 and >60.

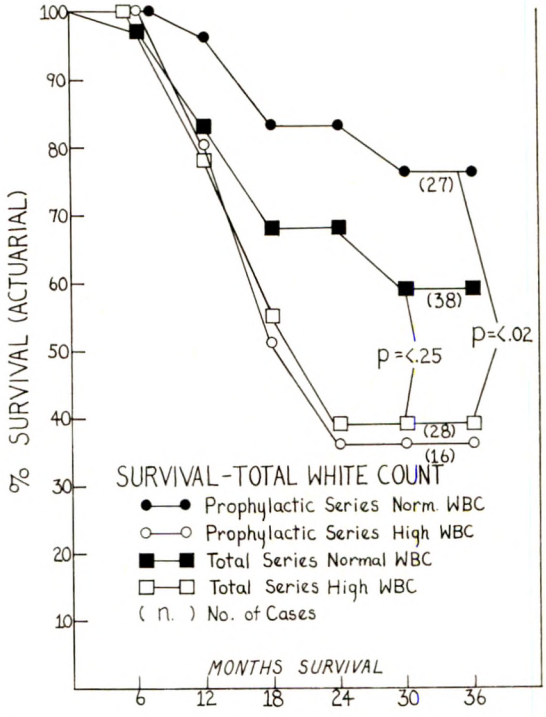


FIG. 9. Elevated white blood cell count (>7,000) provides probable significant difference in non-metastatic cases.

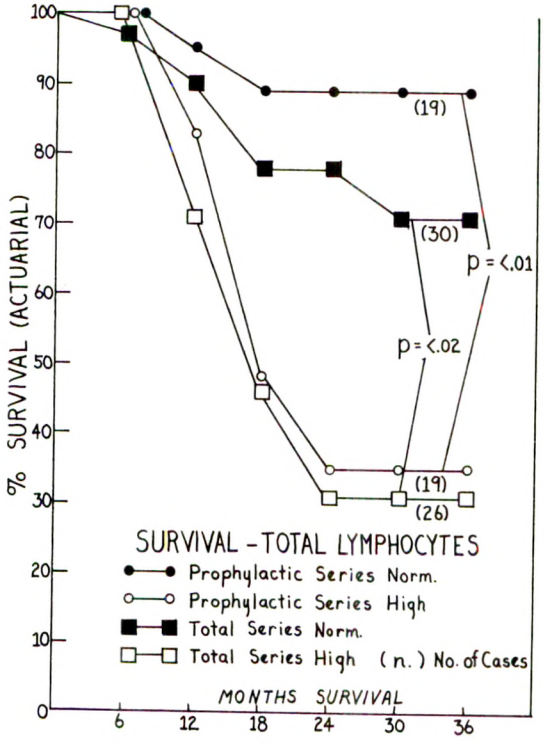


FIG. 10. Total lymphocytes in non-metastatic series provide similar, but more significant change: high >2,000.

DURATION OF SYMPTOMS

Patients with symptoms present for greater than 6 months have enjoyed a moderately improved survival. Median survival is 48 months for those with symptoms longer than 6 months compared to 26 months for those with symptoms less than 3 months. This may be related to less aggressive tumor growth and/or more efficient host defenses. Conceivably, this may prove to be a useful parameter in selecting patients for nonspecific immunotherapy.

PLATELETS

A platelet count initially of over 400,000 indicates a poor prognosis (Fig. 11). This probably is indicative of tumor presence in the bone marrow. Platelet level increases during chemotherapy have been related to development of early bone relapse also indicating an irritative phenomenon of tumor presence. This parameter appears to be holding for the present protocol (Adriamycin, Cytoxan, and Vincristine) and should continue to be useful, whereas many of the parameters have tended to become weakened as prognostic indicators where early survival rates have improved, particularly in the non-metastatic series.

Systemic symptoms, particularly fever have also remained of probable importance in the current protocol (Fig. 12) but will require further time and/or a larger number of cases to determine the actual significance.

HISTOLOGIC HYPERSENSITIVITY

Perivascular infiltration of lymphocytes as seen with skin testing with various antigens including DNCB have been noted in a number of instances in the supporting stroma of Ewing's sarcoma. A rough corre-

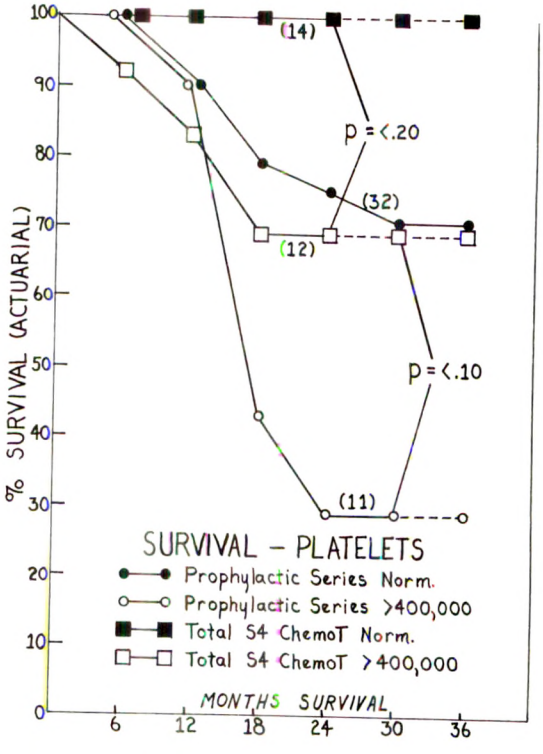


FIG. 11. Platelet count over 400,000 indicates poor prognosis presumably indicating tumor in the marrow. This may prove to be a valuable indicator as it appears to be holding for the current S4 (Series 4) protocol (Adriamycin, Cytoxan, and Vincristine).

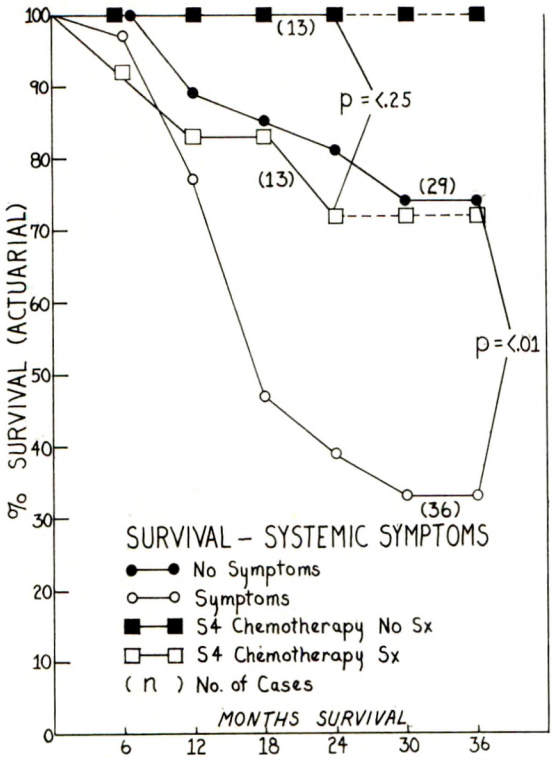


FIG. 12. Systemic symptoms also are holding (although not yet significantly) as a useful indicator in the S_4 protocol.

lation has been found with gross survival and with survival continuously free of disease (Table III). This finding requires further evaluation and correlation with immune competence determinations to ascertain its significance.

However, it may help in selecting patients for trial of nonspecific immunotherapy to be initiated when the total tumor load has been reduced to a minimum by chemotherapy and radiation therapy.

TABLE III

PERIVASCULAR "HYPERSENSITIVITY" REACTIONS AND SURVIVAL IN EWING'S SARCOMA

	HSR^-	HSR^+	HSR^{++}
Total	39	16	6
Alive	15 (38%)	9 (56%)	6 (100%)
CFOD	7 (18%)	6 (37%)	5 (83%)

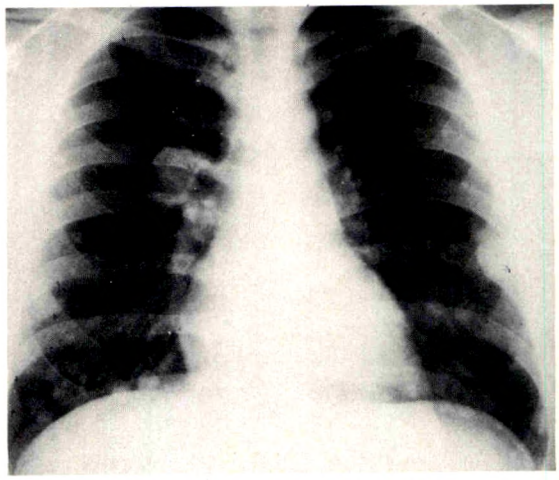


FIG. 13. Chest roentgenogram on admission: 18 year old male with primary tumor of upper femur, HSR^{++}.

The relationship of this finding to tumor response is demonstrated by the cases in Figures 13–17. The first case (Fig. 13; and 14) with HSR^{++} responded much more rapidly and completely to chemotherapy than the second case (Fig. 15; 16; and 17). If HSR is related to host immune reactions with specificity for the tumor, the possibility of enhancement by both non-specific and specific stimulation (such as BCG with and without allogeneic cells) becomes a challenging opportunity.

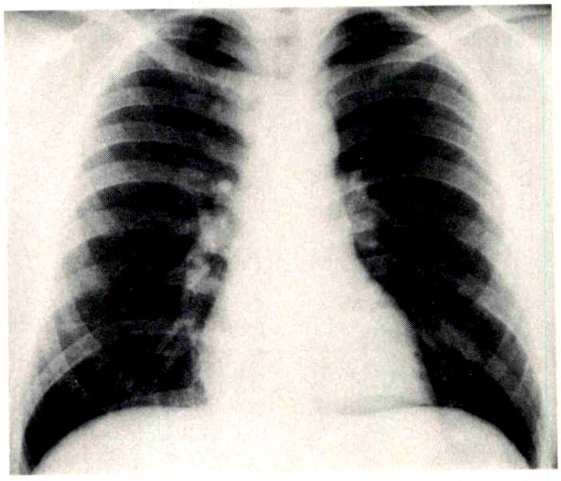


FIG. 14. One month later after single dose of Adriamycin and radiation therapy to primary; tumor response >90 per cent.

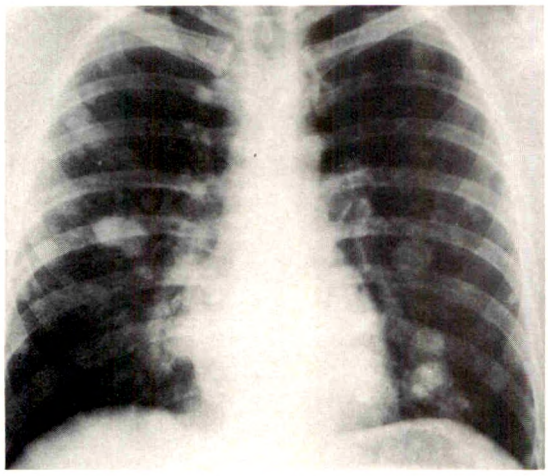


Fig. 15. A 24 year old male with extensive pulmonary metastasis from iliac bone primary, HSR⁻.

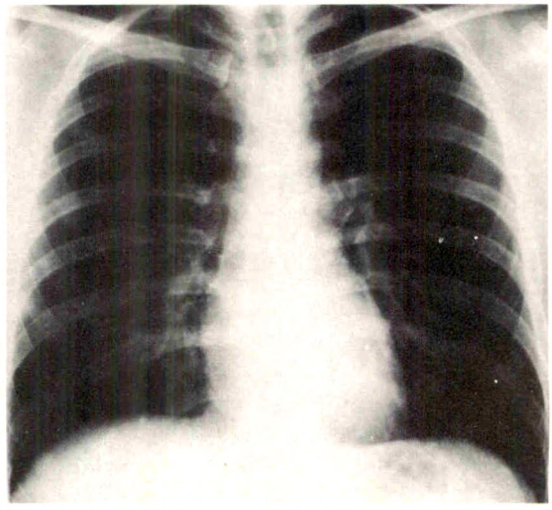


Fig. 17. Eight months later after continued chemotherapy and 2,000 rads whole lung irradiation.

OTHER PARAMETERS

A number of other possible prognostic indicators have been evaluated with no consistent patterns apparent in this series. PAS (periodic acid-Schiff reaction for glycogen) histology of the tumor has had no relationship to survival. Tumor site within a long bone (metaphysis or diaphysis) has no apparent relationship to survival nor does the radiographic appearance (lytic, sclerotic, mixed, or onion skin pattern). Immunoglobulins and immunoelectrophoresis have shown disturbed patterns in many cases but remain of little significance in prognosis.

As described above, age-adjusted (female+4 years) sex has no prognostic value and total male and female survival rates are not significantly different.

The relative importance of the various prognostic factors as determined in this series is tabulated in Table IV. These factors are neither final nor static and as emphasized above are likely to vary with different chemotherapeutic regimens. Hopefully, most of them will be of less and less importance as more effective treatment methods are developed.

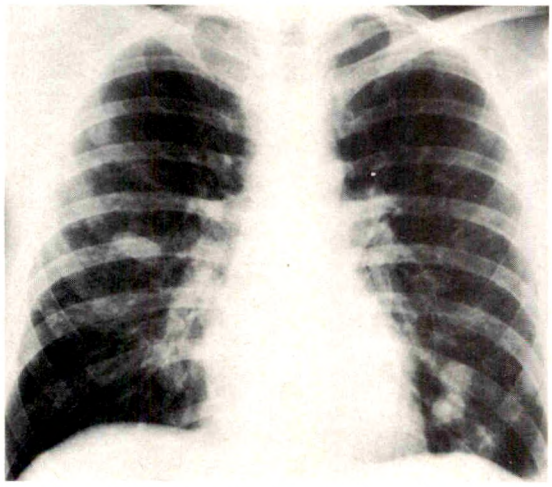


Fig. 16. One month after Adriamycin; some tumor response, but <50 per cent.

Table IV

PROGNOSTIC FACTORS IN SURVIVAL OF EWING'S SARCOMA

Presenting metastasis	+++
Site of primary tumor	++
Age at diagnosis	++
Lactic dehydrogenase	++
Systemic symptoms	++
Duration of symptoms	+
Sedimentation rate	+
Platelets	+
Total white blood cell count	+
Total lymphocytes	+
Sex (age adjusted—female+4 yr.)	—
PAS histology (periodic acid-Schiff)	—
HSR (hypersensitivity reactions)	?

Nonetheless, for the present, it is important to document this information in all instances where systematic treatment approaches are being evaluated. This applies to randomized prospective trials (where some stratification may be applicable) as well as evaluation of sequential series.

An example of the latter is outlined in Table v. This publication compared sequential series where the treatment methods were quite divergent. Although the age and sex ratios were similar, the tumor site distribution was not balanced. Calculation of expected survival if both series had been treated in identical fashion indicates that Series 2 should have a 50 per cent increase in survival over Series 1 if only this one parameter was considered. The same variance in results may obscure or falsely enhance differences in randomized prospective trials if attention is not paid to preliminary stratification or retrospective assurance of balance for the more important prognostic indicators.

SUMMARY

The improvement in survival rates for Ewing's sarcoma by aggressive use of adjuvant chemotherapy has provided an opportunity to evaluate a number of prognostic factors for this improving situation. Analysis of results in 66 consecutive cases admitted to the Radiation Branch of the National Cancer Institute indicates the importance of considering these factors in future treatment planning.

In addition to the presence or absence of clinical metastasis at the time of diagnosis, the site of the primary lesion, the age at diagnosis, and the presence of systemic symptoms (particularly fever) have proved to be reliable indicators of subsequent survival experience.

Other factors of potential importance, but requiring further evaluation and experience, include lactic dehydrogenase levels, duration of symptoms, erythrocyte sedimentation rate, total white blood cell and total lymphocyte levels, platelet determinations, tissue hypersensitivity reactions, and measurements of immune competence. Sex, if adjusted to growth and maturation, has little effect except in relation to menarche, with potential relapse occurring in association with the onset of menstruation.

The importance of consideration of these factors in the planning of future treatment regimens is readily apparent, and emphasizes the need for centralization of treatment of Ewing's sarcoma where such evaluation will be possible in sufficient numbers of patients to help determine the optimum adjuvant therapy regimen for each category of patient and eventually for each individual patient.

TABLE V

THE EFFECT OF TUMOR SITE ON EXPECTED SURVIVAL IN SEQUENTIAL SERIES OF EWING'S SARCOMA (8)

	1st Series	2nd Series
Trunk	8	1
Femur and humerus	5	4
Peripheral locations	5	7
Expected 2 yr. survival if given the same treatment	9/18 (50%)	9/12 (75%)

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OSTEOGENIC SARCOMA (OSTEOSARCOMA): RESULTS OF THERAPY*

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BETWEEN November 1, 1955 and June 30, 1973, 46 patients with osteogenic sarcoma (osteosarcoma) without evidence of metastases were admitted to the UCLA Center for Health Sciences. The follow-up is 100 per cent.

The youngest patient was 5 years of age and the oldest 73; the average age was 26.7 years and the median age 16.0 years; 29 or 60.3 per cent of the patients were between ages 11 and 20 (Table I).

TABLE I

AGE DISTRIBUTION

Age (Years)	No. of Patients
0–4	None
5–10	2
11–20	29
21–30	4
31–40	2
41–50	4
51–60	3
61–73	2
	46

There were 26 males and 20 females. Thirty-five patients were Caucasian, 6 Black, and 5 Mexican American. A peak incidence of osteosarcoma has been noted at about 18 years of age with a sharp drop above this age in series of patients reported in Westminster, Massachusetts General Hospital, Mayo Clinic, and Memorial Hospital. In many reported series, the highest incidence has been noted in patients between 11 and 20 years of age.[9]

The average time period for the appearance of metastases calculated from the onset of therapy was 5.5 months. Of the patients who developed metastases, 87 per cent had metastases within a period of 14 months with the majority appearing in 9 months or less time. The time of appearance of metastases could not be determined in 1 patient because he did not see a physician during the last year of his life; in 1 patient, metastases occurred 6 years and 6 months later (this patient also had 3 other primary malignancies—breast carcinoma, cervix carcinoma, and malignant melanoma); 1 patient had metastases to the lung 8 years and 5 months after the initial therapy; another patient had metastases 3 years and 11 months later.

A history of trauma was given by 13 of the 46 patients as follows: mild in 8; moderate in 3; pathological fracture in 1 with minimal trauma; and 1 patient had a fracture of his femur 30 years previously but no recent history of trauma. Trauma is not considered as an etiological factor in the causation of osteosarcoma. When trauma does occur, it usually directs attention to a pre-existing tumor.

Roentgenographic findings of the primary lesion revealed that the lesions were of the blastic type in 15, lytic type in 17, blastic and lytic in 14. There was evidence of local soft tissue involvement in 34 or 74 per cent of the patients (Table II).

McKenna *et al.*[12] reported the data from the California Tumor Registry from 12 participating hospitals from 1942 to 1969. There were 722 cases of primary malignant bone tumors during that period, representing an incidence of 0.46 per cent of all malignant tumors. They were able to make a personal study of 367 cases and found that the following types of primary malignant bone tumors in decreasing incidence accounted for 95 per cent of all primary

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Table II

BONE INVOLVED

Femur	28
Tibia	4
Humerus	3
Mandible	3
Fibula	1
Ilium	2
Sacrum	2
Frontal bone	1
Sphenoid	1
Maxilla	1
	46

malignant bone tumors: osteosarcoma, chondrosarcoma, Ewing's sarcoma, reticulum cell sarcoma, and fibrosarcoma. The reported 5 year survival for "localized" tumors was given as follows: osteosarcoma, 28.9 per cent; Ewing's sarcoma 18.2 per cent; chondrosarcoma 62.2 per cent; reticulum cell sarcoma 42.9 per cent; and fibrosarcoma 30.8 per cent. Multiple myelomas were not considered in their report. They found that 54.8 per cent were male, 90.6 per cent Caucasian, 6.9 per cent Black, and 2.5 per cent other races. The authors recommended standardization of the staging and the "up-dating" of the classification of bone tumors.

None of the 46 patients in this series had ever received radiation therapy to the area where the osteosarcomas originated. Irradiation has been given as one of the predisposing conditions to the possible development of osteosarcoma. Other possible predisposing conditions are osteitis deformans (Paget's disease), fibrous dysplasia, osteochondroma, and giant cell tumor.

With regard to pre-existing pathology, the 2 patients who also had Paget's disease are deceased, one 3 months after the institution of therapy and the other patient 9 months later. One patient had fibrous dysplasia with multiple fractures involving the left mandible and osteosarcoma. Death occurred in this patient 16 months after the diagnosis of osteosarcoma was made.

Twenty (3.3 per cent) of the 600 osteosarcomas reported by Dahlin and Coventry[4] originated in bone affected by Paget's disease. Three of the 20 patients were long time survivors, 7 years, 7 years, and 12 years. Sixteen of their patients had osteosarcoma which arose in previously irradiated bone. None of these patients lived more than 3 years. Eighty-three (20.3 per cent) of 408 patients who were followed and treated before January 1, 1960 survived 5 years, and 62 (17.3 per cent) of 359 patients who were traced and treated prior to January 1, 1955 survived for 10 years.

McKenna *et al.*[13] reported 33 histologically proven cases of osteosarcoma arising in patients with osteitis deformans (Paget's disease). The 33 cases accounted for 6 per cent of the cases of osteosarcomas diagnosed at Memorial Hospital. They found that only 4 patients with osteosarcoma arising in bones with osteitis deformans survived more than 5 years without evidence of metastasis. The patients were treated by surgery. It has been stated that approximately 0.2 per cent of the patients with osteitis deformans (Paget's disease) will develop sarcomas.[15]

Lee[8] has commented that about 80 per cent of patients with osteosarcoma die usually from lung metastases and that by 10 months after diagnosis of the primary lesion, 80 per cent of the metastases will have occurred.

He believes that since the results of immediate surgery have not been better than those in patients who have had preoperative radiation therapy with delayed amputation in cases remaining free of metastases, that the delay has cost no lives that might have been saved. The trial of preoperative radiation therapy followed by delayed amputation was reported by Lee and Mackenzie[9] in 1964. A total of 187 patients with osteosarcoma were so treated with 41 (21.9 per cent) 5 year survivors.

Preoperative radiation therapy was not recommended for patients who had a fungation of the tumor as a result of the biopsy, if a gross pathological fracture was present,

or if the patient had a flexion contracture of the hip or knee.

Because of 80 three year patients reported by Lee and Mackenzie[9] who eventually developed metastases, 60 or 75 per cent did so within 5 months of completing the preoperative irradiation, they believe that it would be desirable to wait at least 5 months prior to ablation.

The authors presented results to show that the method of adequate megavoltage radiation therapy and elective ablation compares favorably with immediate surgery. They do not believe anything is lost by the delay in ablating the irradiated tumor.

They are of the opinion that the whole bone must be removed in spite of the appearance of the tumor being confined to a limited area because, in their experience, the tumors spread widely in the cancellous portion of the bone.

Among the 20 long-term survivors of 5 or more years reported by Lee and Mackenzie,[9] there were 7 patients or 35 per cent who had remained well from 5 to 11 years and who had radiation therapy only, with tumor doses ranging from 5,750 r in 33 days to 9,000 r in 76 days.

Lee[8] reported that of 21 patients with chondrosarcoma treated by preoperative radiation therapy and delayed amputation, 12 or 57 per cent were alive and well 5 or more years. Lee[8] commented that "Our attitude regarding the osteosarcoma group may be summed up thus: Success is perhaps too euphemistic a word so long as we are treating disseminated disease by local methods, but we would measure our success—such as it is—by the number of futile amputations avoided, and this was achieved in about one-half the cases."

Allen and Stevens[1] reported their experience using preoperative radiation therapy in tumor doses ranging from 7,900 rads to 10,000 rads and planned delayed amputation. Seven patients were treated and 3 are alive at 5 years. Of 20 patients with osteosarcoma of the femur treated by surgery only, only 2 were alive at 5 years.

Francis *et al.*,[5] in studying the amputated specimens in the femur, frequently found that the tumor extended through the marrow cavity for a considerable distance. They reported 10 patients with osteosarcoma of the femur or tibia treated by preoperative radiation therapy with tissue doses of 6,000 r to 12,000 r delivered in 5 to 10 treatments followed in 1 to 2 days by amputation. The results were not encouraging in that of the 10 patients treated during a 2 year period, only 3 were considered to be free of disease at the end of 1 year, 2 were living with metastases, and 5 were dead.

A study concerning medullary extension of osteosarcoma with regard to therapy has been reported by Lewis and Lotz.[10] Twenty cases of osteosarcoma of the long bones representing all amputation specimens from 1959 to 1972 were submitted for study at the National Cancer Institute. All the patients were free of metastatic disease at the time of the amputation. No cases of parosteal osteosarcoma, chondrosarcoma, or primary fibrosarcoma of bone were included.

The correlation between the extent of the tumor as noted on the roentgenograms and on the gross pathological examination was good. There were no local recurrences at the amputation site in the 20 cases. It was noted in 2 cases that the transverse microscopic sections of the bone within 1.0 cm. of the gross tumor revealed direct microscopic extension of the tumor. Sections made at 2.0 cm. from the gross margin and beyond revealed no extension of the tumor. There were no "skip areas." In the other 18 cases, multiple microscopic section examinations revealed no microscopic extension within the medullary canal beyond the gross margin.

They concluded that "no superiority of disarticulation or amputation one joint above to transmedullary amputation has been demonstrated in the literature."

Jenkin *et al.*[7] reported on 22 patients less than 30 years old with the primary site in a limb for which the planned management

was by preoperative radiation therapy and selective delayed amputation. The mean duration of tumor control by radiation therapy was 3.6 months. The tumor recurred in all patients.

They concluded that the palliation obtained was not adequate to justify delay in amputation. In their total experience with the management of 62 patients with osteosarcoma diagnosed during the years 1958–1970 and treated by various methods, the 5 year survival rate was not greater than 5 per cent. They had a 100 per cent recurrence or failure of local control within 6 months after beginning radiation therapy. They considered that the amount of morbidity and local effects of the radiation therapy did not provide adequate palliation or justify its use. Apparently, osteosarcoma in the Toronto region is a very lethal disease. The tumor registry of the Hospital for Sick Children in Toronto reported that of 18 children with osteosarcoma diagnosed at that hospital during the years 1924–1958, there was not a single 5 year survivor, regardless of the treatment.

Phillips and Sheline[14] found that of 23 patients with osteosarcoma treated with preoperative radiation therapy, 5 or 23 per cent were alive at 5 years; of 10 patients who had primary surgery, 1 patient (10 per cent) survived 5 years.

They compared the size of the lesion as noted roentgenographically with the true extent of the tumor in 9 cases. In these cases, the surgical procedure had been performed at distances varying from 5 to 15 cm. proximal to the margin of the lesion as seen on the roentgenograms. In none of the cases was there tumor present at the site of the amputation, and later recurrence at the amputation site was not noted.

Weinfeld and Dudley[19] reported the results of a study of 94 patients with osteosarcoma who were treated at the Massachusetts General Hospital between 1920 and 1960. There was no uniform treatment policy. Lesions located in the skull, spine, and pelvis which could not be excised were treated by radiation therapy. Only 2 patients received roentgen therapy prior to surgical ablation of the tumor. Thirteen patients survived more than 5 years after surgical therapy.

The incidence of primary bone sarcoma at one institution between 1941 and 1961 was reported by Copeland[3] as 0.68 per cent. He reported that early amputation and occasionally radical resection has been the treatment of choice in 121 cases of osteolytic osteosarcoma with a 16 per cent 5 year survival rate and that cures have been obtained in 32 of 163 cases (20 per cent) of osteoblastic osteosarcoma by amputation and in some cases by resection. He was of the opinion that a permanent cure has not been obtained by the use of radiation therapy only.

Twenty-two osteosarcomas were treated by Suit and Lindberg[17] with radiation therapy, administered under conditions of tourniquet-induced local tissue hypoxia. They concluded that the late reactions of normal tissues were so severe after 16,000 rads, that this treatment method was not considered to be a clinically effective method for the therapy of osteosarcomas.

The average 5 year survival results reported from 7 series totalling 926 cases treated by surgery only was 19.8 per cent. The average 5 year survival results from 8 series of 336 cases treated by preoperative irradiation and delayed surgery was 23.25 per cent. The results from treatment by radiation therapy alone is less than by either surgery only or preoperative irradiation and delayed surgery.

There is apparently very little difference in the chance of survival in osteosarcoma, whether the primary treatment is immediate amputation or if preoperative radiation therapy is given followed by amputation in approximately 6 months.

The plan at the UCLA Center for Health Sciences has been on an elective basis to give preoperative megavoltage irradiation, 6,000 to 7,000 rads tumor dose at the rate of approximately 900 rads tumor dose per week to the whole limb or bone involved

TABLE III

LONG-TERM SURVIVORS: OSTEOSARCOMA

Patient	Age (Years)	Site	Symptoms (Months)	Therapy	Comment	Result
1. G.L.	16	Sacrum	18 mo.	Radiation therapy	Alive and free of disease	4 years, 3 months
2. A.S.	26	Mandible	3 mo.	Radiation therapy, surgery, and chemotherapy	Alive and free of disease	9 years, 8 months
3. D.H.	60	Femur	48 mo.	Radiation therapy and hip disarticulation	Alive and free of disease	12 years, 6 months
4. L.O.	71	Femur	2 mo.	Radiation therapy	Alive and free of disease	4 years, 8 months
5. V.C.	16	Femur	5 mo.	Radiation therapy and resection	Alive and free of disease	6 years, 6 months
6. S.W.	19	Femur	5 mo.	Radiation therapy	Alive and free of disease	10 years
7. J.H.	14	Femur	1 mo.	Radiation therapy and hip disarticulation	Alive and free of disease	11 years, 1 month
8. J.S.	12	Femur	2 mo.	Radiation therapy and hip disarticulation	Free of disease 8 years, 5 months. Developed metastases to lung. Surgery. Free of disease now.	8 years, 9 months
9. J.B.	20	Tibia	1 mo.	Radiation therapy and mid thigh amputation	Alive and free of disease.	8 years, 6 months
10. E.H.	20	Tibia	1½ mo.	Radiation therapy and mid thigh amputation	Had primary carcinoma of breast, primary carcinoma of cervix, and primary malignant melanoma. Lived 4 years, 5 months free of disease and then 4 more years before death from metastases from osteosarcoma.	8 years, 5 months, death with disease
11. M.B.	22	Mandible	6 mo.	Radiation therapy and chemotherapy	Lived 3 years, 11 months free of disease. Developed metastases to lungs and died 5 years, 11 months post diagnosis.	5 years, 11 months, death with disease

and then to consider surgical ablation 4 to 6 months later.

Of the 46 patients admitted with "localized" disease, there have been 11 long-term survivors. There were no 5 year survivors from surgery only. There were 3 long-term survivors from radiation therapy only; 6 who were treated by radiation therapy and surgery; 1 treated by radiation therapy, surgery, and chemotherapy; and 1 who had radiation therapy and chemotherapy (Table III).

When patients with osteosarcoma are first seen after usually a very short history averaging 2.5 months, the local lesions are usually large. Osteosarcoma represents systemic disease and whether the local lesion is treated by immediate amputation or by preoperative irradiation followed by delayed amputation is only a part of the problem. Systemic disease requires systemic therapy. It has been amply proven that preoperative irradiation and delayed ablation is just as effective as immediate amputation. If the end results are to be improved from the survival of approximately 20 per cent for 5 years, then planned studies involving systemic therapy must be instituted. The same is true for Ewing's sarcoma where local surgery or radiation therapy can effectively control the local disease but uniformly poor results have been obtained because local measures can cure local disease but will not control systemic disease.

Encouraging results have been reported following local radiation therapy (6,000–7,000 rads) followed by 4 drug adjuvant

chemotherapy for Ewing's sarcoma (actinomycin D, adriamycin, vincristine, and cyclophosphamide) by Rosen *et al.*[16] Ewing's sarcoma of bone must be considered as a disease with early systemic spread. Investigations are in progress combining chemotherapy with other methods of therapy for osteosarcoma. Hopefully, effective chemotherapeutic drug combinations will be found since the present 20 per cent 5 year survival rate obtained by the use of surgery alone or when combined with preoperative radiation therapy is not adequate for this disease.

Multi-drug adjuvant chemotherapy at the M. D. Anderson Hospital using cyclophosphamide, oncovin, phenylalanine mustard and adriamycin following amputation has given encouraging results. Prior to adjuvant chemotherapy, the survival rate in 33 children with osteosarcoma was 6 per cent. Eighteen patients have been treated with multi-drug therapy following amputation and 8 have developed metastases, 3 to 12 months from the time of amputation. Ten of the patients or 55 per cent still remain free of disease 20 months or longer. Studies are continuing and further studies with the multi-drug therapy plus methotrexate and citrovorum factor rescue may give improved results.[3,18]

Marcove *et al.*,[11] in a preliminary report concerning the use of vaccine in patients with osteosarcoma, made the following comment: "Twenty-one patients with osteogenic sarcoma of the long bones treated by a lysed cell vaccine, in addition to routine amputation, appear to have an encouraging response to vaccine treatment, compared with both the whole cell vaccine and the control series." Their data suggest that there is clinical evidence of immunologic manipulation of a human tumor.

SUMMARY

Between November 1, 1955 and June 30, 1973, 46 patients with osteosarcoma without evidence of metastases were admitted to the UCLA Center for Health Sciences. The follow-up was 100 per cent.

The plan for therapy after biopsy has been to give preoperative megavoltage radiation therapy, 6,000 to 7,000 rads tumor dose at the rate of 900 rads per week to the whole limb or bone involved and then to consider surgical ablation 4 to 6 months later, if metastases have not occurred.

The average duration of symptoms was 2.5 months, and the average time period for the appearance of metastases calculated from the onset of therapy was 5.5 months. Eighty-seven per cent had metastases within a period of 14 months after diagnosis with the majority appearing usually in the lungs in 9 months or less.

There have been 11 long-term survivors. There were no 5 year survivors from surgery only. There were 3 long-term survivors from radiation therapy only; 6 who were treated by radiation therapy and surgery; 1 treated by surgery, radiation therapy, and chemotherapy; and 1 who had radiation therapy and chemotherapy.

It is believed that maximum results which can be obtained from surgery alone or from preoperative radiation therapy plus ablative surgery have been achieved, and the results are approximately 20 per cent 5 year survivals. Since osteosarcoma is a systemic disease and because of the brief period of symptoms and rapid onset of metastases following therapy, any further improvement in survival statistics will have to be the result of additional therapy directed to the prevention of systemic spread of the disease. There are some cases of osteosarcoma which represent localized disease, possibly 5 to 15 per cent, but there is no method to determine which ones they are at the present time prior to the initiation of therapy.

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RADIOLOGIC MANIFESTATIONS OF NORTH AMERICAN BURKITT'S LYMPHOMA*

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AFRICAN Burkitt's lymphoma has been a well recognized entity since its original description by Burkitt in 1958.[1] It was further elaborated upon by others shortly thereafter.[3,12,13] The x-ray findings have also been noted.[4,5,8,16–19] Additional reports demonstrated the disease to be more widespread than originally suspected.[2,4,7,9,14] Cases have been reported in North America in which, although the clinical picture varied from African Burkitt's lymphoma, the microscopic pathology was identical.[6,10,15]

We wish to describe the radiologic findings in several patients we have studied with the North American form of Burkitt's lymphoma, and compare them with the findings seen in African Burkitt's disease.

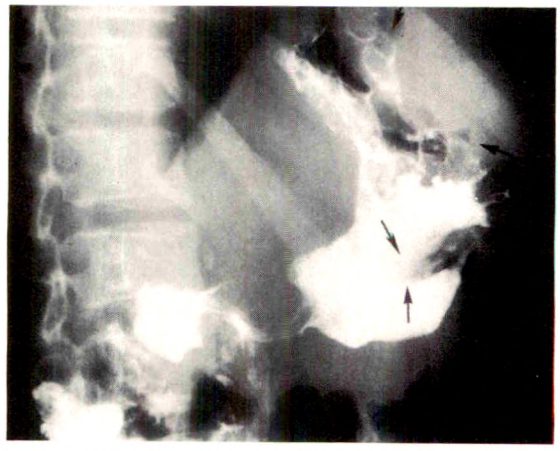

FIG. 1. *November 5, 1971.* Multiple filling defects and thickened mucosal folds in the fundus and body of the stomach.

REPORT OF CASES

CASE I. The patient was a 16 year old Caucasian male who presented with a recent onset of dyspnea. Physical examination demonstrated a large tonsillar mass, and orthostatic hypotension. All laboratory data were within normal limits. A biopsy from the tonsillar mass was compatible with Burkitt's lymphoma. The tonsillar mass was treated with external irradiation with complete regression. About 2 months later the patient developed mid-epigastric pain. An upper gastrointestinal series was abnormal (Fig. 1). A follow-up lymphangiogram was also abnormal (Fig. 2). The remaining laboratory studies were normal. Treatment with cytoxan resulted in complete resolution of the lymphomatous involvement of the stomach (Fig. 3, *A* and *B*). However, during treatment the patient developed back pain and testicular enlargement. About 5 months later he developed both third and fifth cranial nerve paresis. A cerebrospinal fluid examination showed lymphoma cells. Therapy including intrathecal cytoxan, methotrexate and whole brain and spinal axis irradiation was begun. However, the patient progressively worsened and expired shortly after treatment was initiated.

Autopsy revealed generalized involvement of lymph nodes, stomach, pancreas, diaphragm, epicardium, testes, kidney and central nervous system with Burkitt's lymphoma.

CASE II. The patient is a 21 year old Caucasian female who had a right lower wisdom tooth removed because of surrounding irritation. Several weeks later the site of the tooth extraction showed poor healing and was subsequently seen by a surgeon, who curetted the area and obtained granulation tissue. She underwent a second curetting shortly thereafter because of persistence of poor healing. Biopsy on this occasion was interpreted as lymphoma, or possible leukemia. She was referred to Georgetown University Hospital about 2 months after her initial symptoms began,

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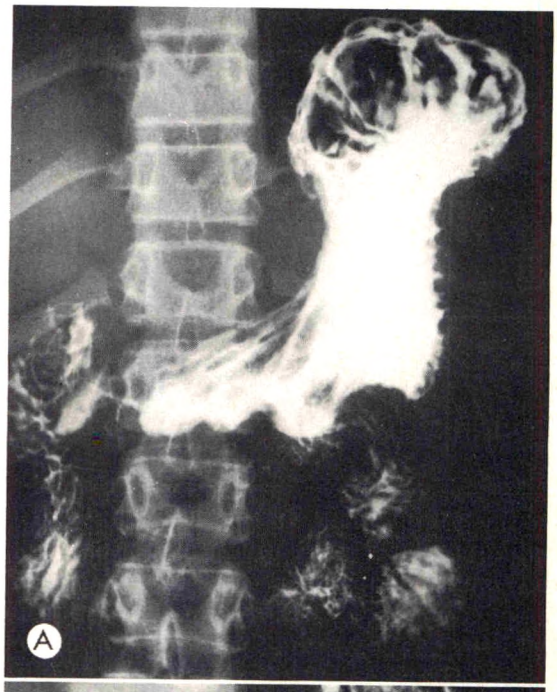
Fig. 3. (*A*) *November 19, 1971.* (*B*) *January 11, 1972.* Follow-up examinations after medical treatment show progressive and eventually complete disappearance of thickened mucosal folds and filling defects in the stomach.



where over the course of the next several months she underwent evaluation consisting of diagnostic mandible roentgenograms, which initially were normal but gradually became abnormal (Fig. 4, *A* and *B*). Initial mandible biopsies at Georgetown were unremarkable but a swelling developed on her right jaw 4 months after her initial symptoms. Biopsy of this revealed a diagnosis of Burkitt's lymphoma. A subsequent intravenous pyelogram and lymphangiogram were abnormal (Fig. 5; and 6).

An exploratory laparotomy was done to evaluate the pelvis because of the abnormal intravenous pyelogram. Burkitt's tumor involving the left ovary was found.

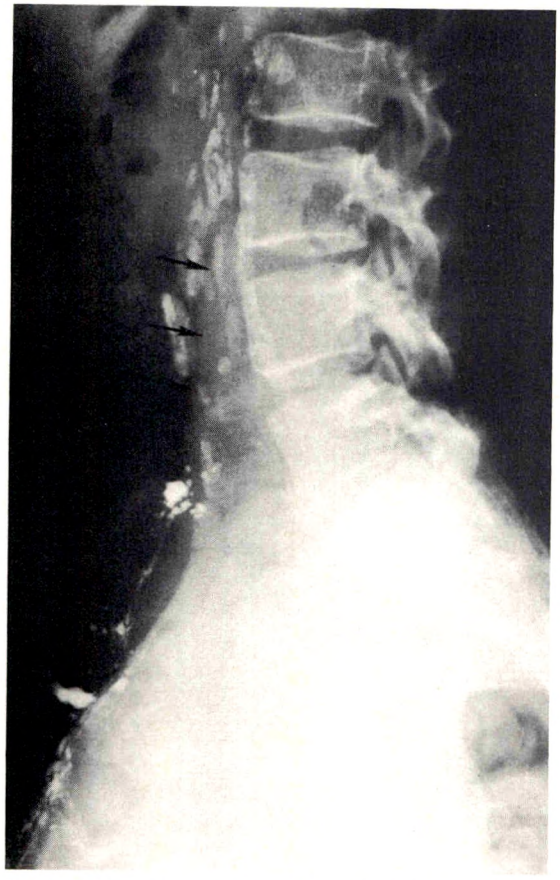


Fig. 2. *November 11, 1971.* Lymphangiogram shows displacement of the lymph nodes by extranodal masses.

Treatment was begun about 6 months after her initial symptoms and consisted of right mandibular irradiation with rapid clinical improvement. Chemotherapy was also started. All therapy was completed within 2 months and

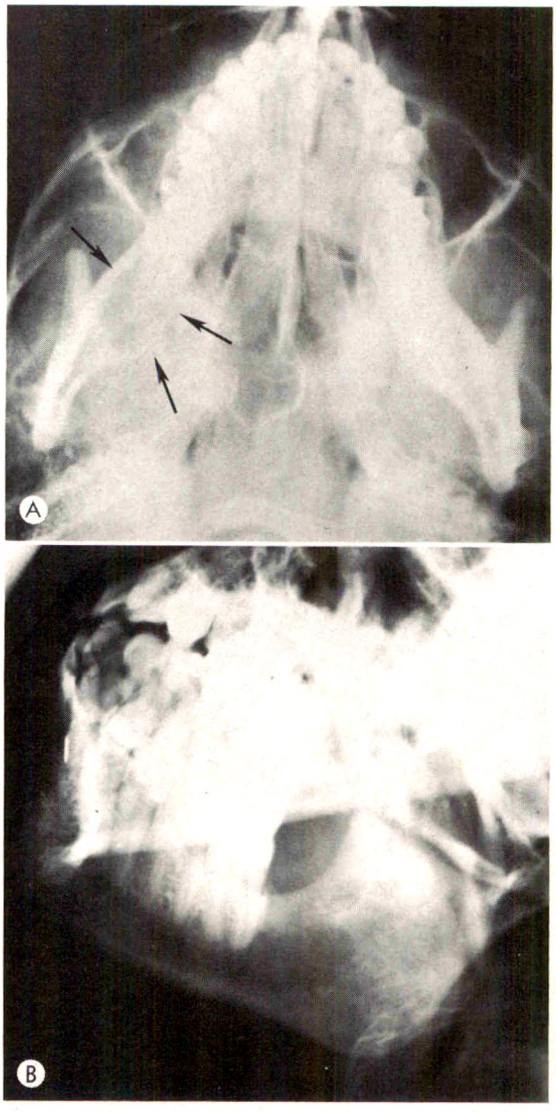


FIG. 4. (*A*) *November 6, 1973.* (*B*) *November 6, 1973.* Expanding lytic lesion present in the body of the right side of the mandible.

the patient has done well since then.

A roentgenogram of the right side of the mandible is shown in Figure 7 soon after therapy.

Of interest is that the patient also has neurofibromatosis manifested by café au lait spots and subcutaneous neurofibromata.

CASE III. The patient was a 49 year old Caucasian male who developed sudden onset of severe abdominal pain, abdominal distention, and melena. Physical examination revealed no palpable mass or peripheral lymphadenopathy. A small bowel examination with barium demonstrated a mass displacing the small bowel with an associated stricture at the jejunoileal junction. The jejunum proximal to the mass was dilated (Fig. 8, *A* and *B*). A laparotomy was performed confirming a 5 cm. polypoid and ulcerated mass with an associated intussusception. There was a suggestion of lymph node enlargement in the mesentery. The involved bowel and lymph nodes were resected. Examination of the resected specimen was compatible with Burkitt's lymphoma. The patient was treated with cytoxan and allopurinol. About 5 weeks following surgery the patient developed a 25 cm. abdominal mass, which diminished in size following another course of chemotherapy. Three weeks later the patient developed a large right flank mass extending from the iliac crest to the

FIG. 5. *December 19, 1973.* Left ovarian mass displacing the left ureter laterally, and the bladder inferiorly.

right axilla, an epigastric mass, and right pleural effusion (Fig. 9). The flank and abdominal masses disappeared following an additional course of treatment with cytoxan, vincristine and prednisone. The right pleural fluid persisted and the patient continued to deteriorate and died several months later.

DISCUSSION

Clinical similarities and differences between the African and North American form of Burkitt's lymphoma have been described in some detail.[6,15] The widespread roentgenographic involvement described in the African form of Burkitt's disease can also be seen in North America as surmised from the scattered cases described as well as from our own limited experience.

Abdominal symptoms appear to present to the clinician most frequently in North America[1] and thus also to the radiologist. The abdominal symptoms may be related to gastrointestinal involvement, as in 2 of our patients. Roentgenographically the involvement of the gastrointestinal tract can be at any location, although the ileum was most affected in the patients studied by Cohen *et al.*[6] Well defined and circumscribed lesions are most common.[11]

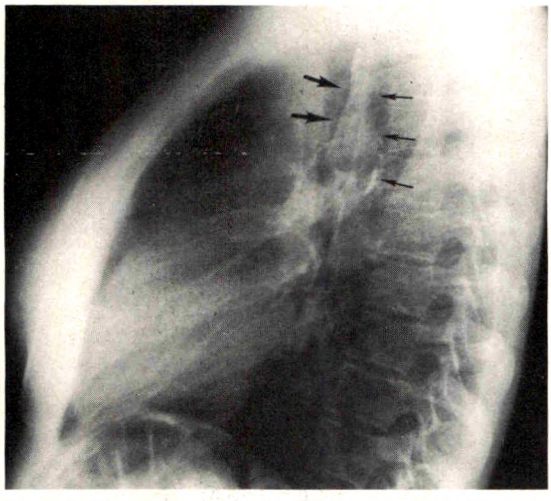


FIG. 6. *December 21, 1973.* Note tracheal displacement anteriorly and posterior displacement of ethiodol filled thoracic duct in lymphangiogram. The displacement is thought to be due to lymphadenopathy.

FIG. 7. *February 8, 1974.* Sclerosis and calcium deposition in the previously present pure lytic mandibular lesion following treatment with irradiation and chemotherapy.

Of the patients we have studied, there was involvement of the stomach in 1 by multiple well-demarcated smooth masses, and in another there was a mid small bowel mass with an associated intussusception (Fig. 1; and 8, *A* and *B*). The lesion may be either large or small, single or multiple.

In African Burkitt's disease the gastrointestinal tract can be involved anywhere throughout its entire extent by variable sized infiltrates in the walls. The liver and pancreas can also be affected.[4,5] Szczygiel[16] believed, however, that most gastrointestinal involvement was seen in the stomach and duodenum. Intussusception has been described in both the African form of Burkitt's disease and the North American form. The large masses noted in the stomach in one of our patients can also be found in African Burkitt's disease.

A relatively small percentage of patients with African Burkitt's lymphoma will manifest abdominal and especially gastrointestinal disease,[16] while the reverse is true for the North American form of Burkitt's disease.

Ovarian masses have been described in African Burkitt's lymphoma.[4,18] It is also a well recognized feature of North American Burkitt's lymphoma.[6] One may see such

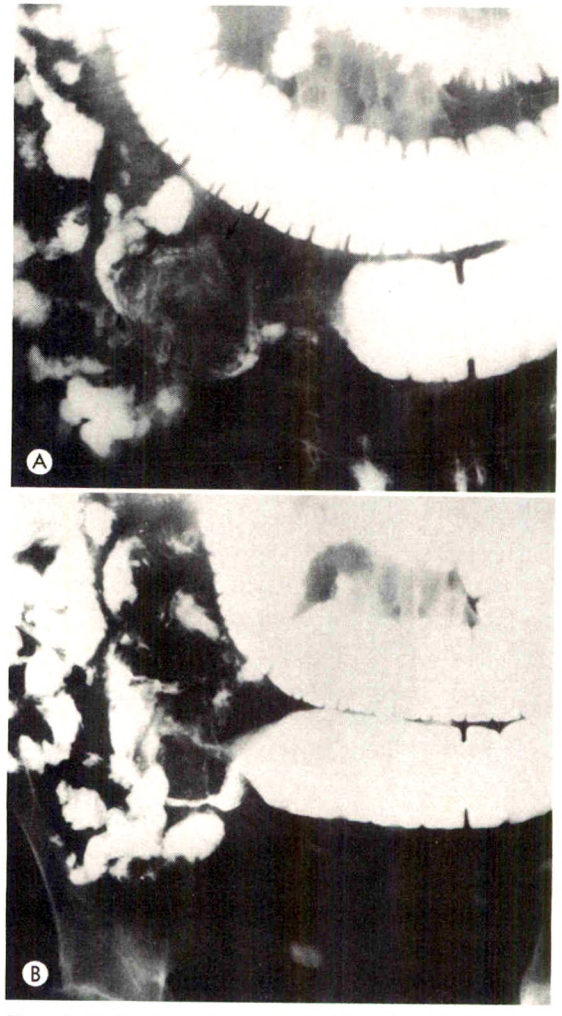


FIG. 8. (*A*) *August 29, 1972.* (*B*) *August 29, 1972.* Four and one-half centimeter mass displacing the small bowel with an associated 3 cm. stricture in the region of the jejunoileal junction.

massive enlargement at the involved ovary that there is secondary bowel and/or bladder displacement and distortion. Figure 5 demonstrates just such an abnormality from our own experience.

Although there was ureteral deviation and bladder distortion by tumor mass in 1 of our patients, as noted in Figure 5, we saw no other evidence of urinary tract disease in our patients. Retroperitoneal disease by tumor mass displacement was demonstrated (Fig. 2). In African Burkitt's disease extensive abnormalities have been described involving the kidneys by primary tumor masses, as well as extrinsic compression of the ureters and bladder. The shape of the bladder in African Burkitt's disease has also been felt to be abnormal and possibly secondary to neurologic involvement.[18,19] It should be stressed that an intravenous pyelogram is of great help in evaluation for both renal as well as ovarian involvement because they may be clinically silent.

In the chest extensive pulmonary parenchymal disease is not seen, but lymphadenopathy including mediastinal and hilar involvement as well as cardiac deposits have been noted in African Burkitt's lymphoma. It is rare to see pleural effusion and when present could indicate cardiac involvement.[5] Cohen *et al.*[6] noted that pleural effusion is more common in the American form of Burkitt's disease. One of our cases demonstrated pleural fluid (Fig. 9). No cardiac involvement was noted clinically during the patient's life. We also demonstrated chest involvement with lymphadenopathy as shown in Figure 6.

Bone involvement, especially of the jaw, which is the hallmark of African Burkitt's lymphoma, occurring in over 50 per cent of patients, does occur in the patients found in North America, but much less commonly.[5,6] Of the American patients described by Cohen *et al.*,[6] 20 per cent manifested jaw lesions. Of our patients, 1 of 3

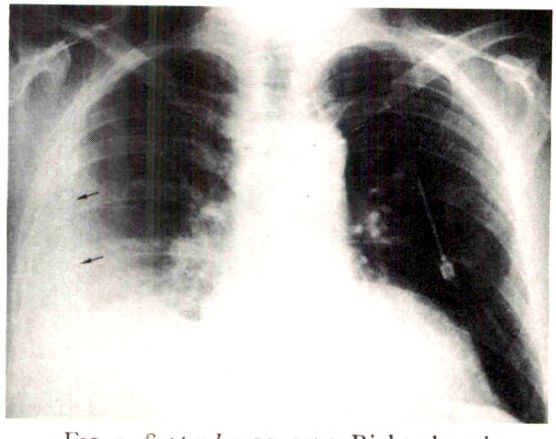


FIG. 9. *September 12, 1972.* Right pleural effusion is demonstrated.

developed a jaw lesion. The appearance of the affected bone is similar to the African and American forms of Burkitt's lymphoma. There are small osteolytic foci in the medullary cavity which progressively enlarge and coalesce (Fig. 4, *A* and *B*). The lamina dura of the teeth is found to be eroded quite early. As the osteolytic focus enlarges, it erodes the cortex stimulating periosteal reaction. Secondary soft tissue swelling is then seen clinically.

Other bone sites may be affected by African Burkitt's lymphoma, and demonstrate a nonspecific lytic appearance. It has also been noted in American Burkitt's disease but is rare.[6]

Following treatment in African Burkitt's lymphoma one sees tumor mass regression and restoration of the teeth to normal position if the disease is in the jaw. The bone density may increase and the trabecular pattern may return.[19] We noted on treatment follow-up a developing bony sclerosis with calcium deposition in the previously lytic zone (Fig. 7). Thus the healing roentgenographic picture between African and American Burkitt's lymphoma is similar.

Central nervous system disease, which is well known in Burkitt's African lymphoma, occurring in perhaps 20 per cent or more of cases, is much less common in American Burkitt's lymphoma.[4,6] In African Burkitt's lymphoma extradural masses have been described in spinal lesions and avascular masses have been noted in intracranial lesions on angiography. Lytic bony deposits have also been described, as noted in other bones. Such findings have not been noted in American Burkitt's lymphoma as yet.

Extracranial angiography in American Burkitt's lymphoma patients has also not been described, although it is well documented in African Burkitt's lymphoma as relatively avascular masses.[5]

Lastly, peripheral lymphadenopathy may occasionally be detected roentgenographically, and it has been noted that peripheral lymphadenopathy is much more common in American than African Burkitt's lymphoma.[6]

SUMMARY

Several cases of Burkitt's lymphoma occurring in North American patients are described from the roentgenographic standpoint. They are used to illustrate similarities and differences, when compared to the roentgenologic findings of African Burkitt's lymphoma. Distinction between them can be summarized as follows:

1. Abdominal disease is more frequent in the North American form of Burkitt's lymphoma, while jaw lesions predominate in the African form of the disease.
2. Pleural effusion is found in American Burkitt's lymphoma and is very rare in African Burkitt's lymphoma.
3. Peripheral lymphadenopathy, which is more common in American Burkitt's lymphomas, is rare in African Burkitt's lymphoma, and although primarily a clinical finding, may be observed by the radiologist.
4. Central nervous system disease and corresponding roentgenographic findings are less common in American as compared to African Burkitt's lymphomas.

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REGIONAL LYMPHADENECTOMY AND TUMOR CURABILITY*

EXPERIMENTAL OBSERVATIONS IN A MURINE LYMPHOSARCOMA

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TUMOR specific or associated antigens have been reported in many animal tumors[25] and some human neoplasias.[17,26] This has led to an increasing emphasis on the importance of a competent immune response of the host in tumor control.[5,18,24,36] The immunological protection that has been postulated is probably cell mediated. Although antitumor sera have been shown to inhibit tumor growth,[2,21] some authors have noted antibody-mediated immunity to induce tumor growth enhancement, probably because of a blocking of cell-mediated protection by antigen-antibody complexes.[34]

The regional lymph nodes and afferent lymphatics have been shown to be a critical component of the immunological system.[7,11,24,27,38] Whereas some authors have reported significant loss of immunological protection with surgical removal of regional lymph nodes and lymphatics,[7,11,12,27] others have not observed this detrimental effect.[3,14,16,18,30] From a clinical viewpoint, there is still a great deal of controversy regarding the removal or irradiation of regional lymph nodes not clinically involved by tumor.[6,32,33,35,37]

The experimental findings reported herein strongly support the postulate that the regional lymph nodes and afferent lymphatics are critical in the initiation of the immune response. Once immunity becomes systemic, their importance in maintaining immuno-protection diminishes substantially.

MATERIAL AND EXPERIMENTAL METHOD

TUMOR TRANSPLANTATION IN MICE

The experiments were performed using the 6C3HED Gardner lymphosarcoma, which has been passaged weekly by a subcutaneous injection of 10^6 cells as a monodispersed suspension into the flank of C3H/Anf inbred mice.* The medium used to prepare the tumor cell suspension was α-MEM† buffered with 20 mM. morpholinosulphonic acid, supplemented with 20 per cent fetal calf serum† and penicillin-streptomycin. The tumors were dissected using sterile technique, minced in the medium and passed through a fine mesh stainless steel screen. After centrifugation at 200 g. for 10 minutes, the supernatant was discarded and tumor cells resuspended in medium. The number of cells was determined using an electronic cell counter and appropriate cell dilutions were made to obtain the desired number of cells for transplant. A subcutaneous injection of .1 ml. was performed in the flank of C3H/Anf 12 to 20 week old mice.

TECHNIQUES OF TUMOR IRRADIATION

Local irradiation was used to achieve control of the tumor as previously described.[27] After cell injection, the tumors were allowed to grow for 3 days (5 mm. in diameter), and at that time, local irradiation was given to the tumor-bearing flank

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with a 220 kvp. x-ray unit, operated at 15 ma. with 2 mm. Cu HVL, which delivered approximately 400 rads per minute at 21 cm. The animals were shielded with appropriate lead blocks, such that the whole-body exposure, including the regional lymph nodes, was less than 1 to 2 per cent of the tumor dose.

REGIONAL LYMPHADENECTOMY

At different times before or after local irradiation of the tumor, with the mice under general anesthesia, the ipsilateral anterior and posterior axillary, as well as the inguinal lymph nodes, were removed using sterile technique. Sham lymphadenectomy was performed in a group of 30 mice 3 days after tumor transplantation, immediately following the local irradiation of the tumor-bearing flank. The procedure consisted of dissecting the skin and subcutaneous tissues, as in the mice having lymphadenectomy, but without removal of the lymph nodes.

BIOASSAY OF TUMOR CELLS IN THE LYMPH NODES

Previous experiments have shown that the time to palpability is a function of the number of viable tumor cells injected.[28] This parameter can be used to estimate the number of cells present in a test inoculum. The lymph nodes removed from tumor-bearing mice were prepared as a monodispersed cell suspension in 2 ml. of medium, and 0.2 ml. was injected subcutaneously into the flank of normal recipient C3H/Anf mice. Approximately 10 animals were assayed every time. In each instance, a recipient mouse was used for each donor, which allowed the identification of the status of the lymph nodes in treated mice with either controlled or recurrent tumors.

EVALUATION OF RESPONSE

All the mice irradiated to the tumor were placed in plastic cages, in groups of 10, with water and food *ad libitum* and examined by palpation every other day, for at least 60 days or until death. The site and time of tumor recurrence in the treated mice and the time of tumor appearance in the recipients of the lymph node suspensions (removed from lymphadenectomized mice) were recorded. Mice used for bioassay were housed similarly and checked daily for at least 3 weeks. The results were tested for statistical significance by the chi-square test or by determining the 95 per cent confidence limits.

RESULTS AND INTERPRETATION

An experiment reported previously[27] showed that the removal of the regional lymph nodes shortly before, at the time of, or within a week from tumor transplantation, significantly interfered with the curability of the lymphosarcoma implanted in the flank of the mice and treated with a single dose of radiation (4,000 rads). A high incidence of both local and axillary recurrences was noted, when the animals were lymphadenectomized a few days before or after the tumor transplantation.

In order to rule out the possibility that the failures in the axillary tissues were the result of mechanical spillage of tumor cells and not a derangement of the immunological response of the host, the following experiment was performed. Monodisperse tumor cell suspensions (10^6 cells in 0.1 ml.) were injected subcutaneously in the flank of C3H/Anf mice, and the tumor-bearing flank was irradiated 3 days later with a single dose of 4,000 rads. Mice with no evidence of tumor recurrence for at least 45 days were injected with 10^6 tumor cells in the opposite flank and given a single dose of 4,000 rads 3 days after transplantation.

At various times before or after transplantation, the regional axillary and inguinal nodes on the side of the second injection were surgically removed. Control groups of normal, not previously immunized animals were treated in a similar manner and regional lymphadenectomy was carried out at similar times. Two other control groups consisted of mice irradiated to the tumor-bearing flank without manipulation of the lymph nodes, and others given a sham

lymphadenectomy, without removal of the lymph nodes.

The animals that had not previously been exposed to the 6C3HED lymphosarcoma showed an appreciable decrease in the cure rates when a lymphadenectomy was performed, in comparison with non-lymphadenectomized or sham lymphadenectomized control groups. This effect was more severe when the removal of the lymph nodes was performed within 4 days prior to or up to 10 days following tumor transplantation (Fig. 1). After this time, the lymphadenectomy did not significantly influence the cure rates. In contrast, the animals that had been previously cured of the tumor and are presumed to have some immunological protection showed a very minimal decrease in the cure rates after removal of the regional lymph nodes in comparison with the control groups.

The analysis of failures showed that the local recurrence rate in the previously cured mice was significantly lower than in the nonimmunized animals (Fig. 2). These results are at variance with others previously reported[27] in which the incidence of axillary recurrences was higher than the local failures. This difference is thought to be due to the use in the current experiment of tumor cell suspensions (10^6), whereas in the previous experiment, tumor chunks were employed, probably yielding a higher cell inoculum (10^7 cells). A larger number of tumor cells migrating to the regional lymph nodes in the latter case may have overcome an incipient immune response.

A bioassay showed that shortly after tumor transplantation, viable tumor cells are demonstrated in the anterior axillary nodes of only 20 per cent of the mice previously cured of tumor (Fig. 3). This

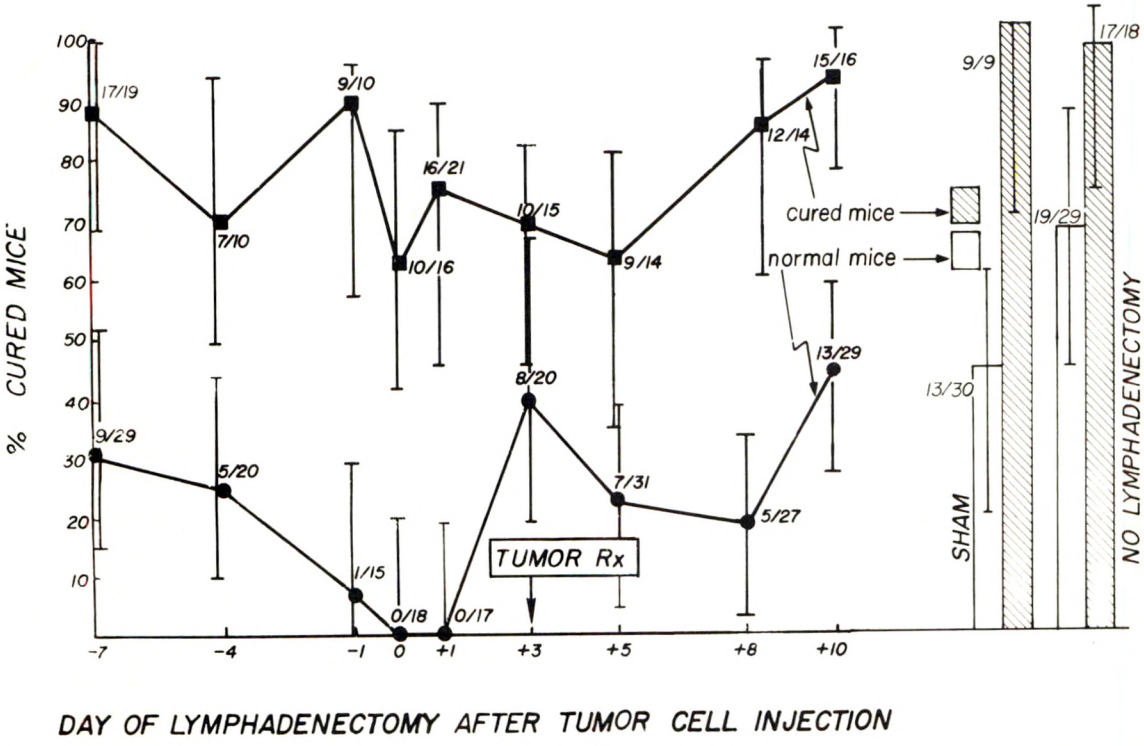

Fig. 1. Cure rates of a murine lymphosarcoma in mice previously cured of the same tumor in comparison with normal animals. Lymphadenectomies were performed at various times before or after tumor transplantation. There is no significant variation in the cure rates of the cured mice following lymphadenectomy, as opposed to a marked decrease noted in the normal mice. Ninety-five per cent confidence limits indicated by vertical bars.

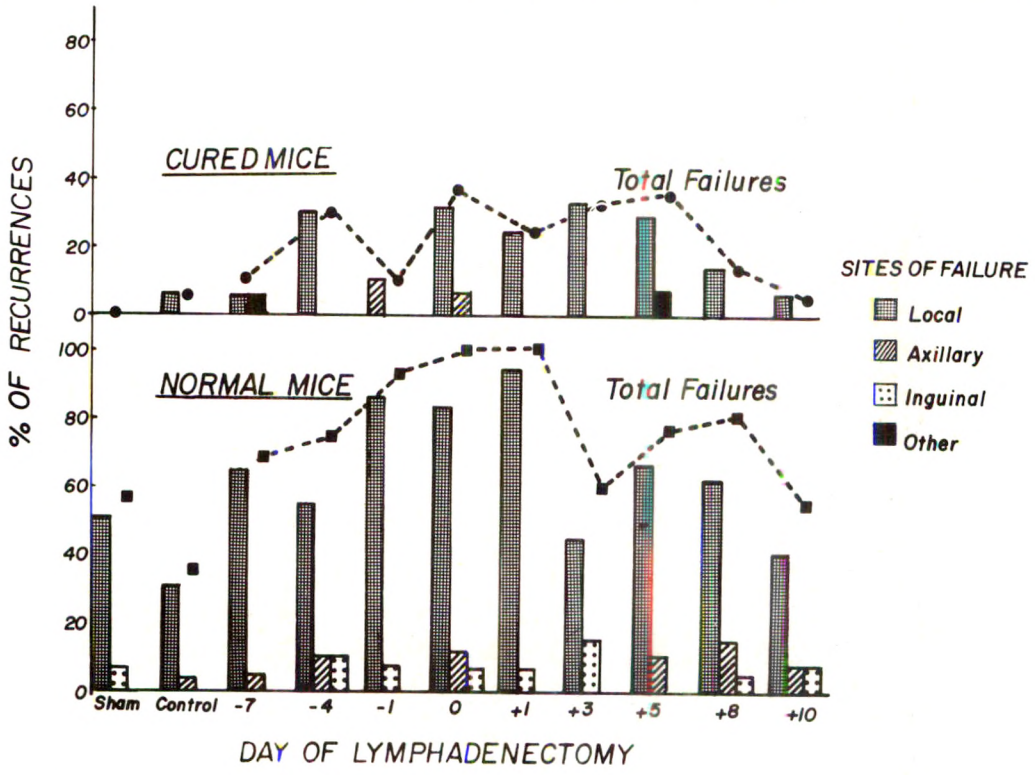

FIG. 2. Sites of recurrent tumor in previously cured or normal mice treated to a transplanted lymphosarcoma in the flank of the animal. A very low incidence of local or axillary failure is noted in the previously cured mice.

is in contrast to a previous experiment, when the animal was not treated, in which the tumor grew unabated and practically all the lymph nodes became positive by Day 5 and remained so throughout the life of the animal. When the tumor-bearing flank was treated, the lymph nodes remained positive for 2 or 3 days and then became negative (data pooled from two separate experiments).

EFFECT OF LYMPHADENECTOMY IN TUMOR CURE WITH VARIOUS CELL INOCULA

Different numbers of tumor cells (10^3, 10^4, 10^5, 10^6) were injected into the flank of normal C3H/Anf mice. Three days later, the tumor-bearing flank was given a single dose of 4,000 rads. Lymphadenectomies were performed at various times prior to or after tumor transplantation.

Figure 4 shows that the mice injected with 10^3, 10^4 or 10^5 tumor cells were always cured of their tumors, and that at the times tested, a regional lymphadenectomy did not have a detrimental effect on their curability. From previous experiments, it has been shown that this dose of radiation is adequate to sterilize these numbers of cells, so that few, if any, cells survive after irradiation.[28]

In contrast, the mice receiving 10^6 cells showed a marked decrease in tumor cures when the regional lymph nodes were removed shortly after tumor transplantation. However, after 8 days, the cure rates are equal to those in the control groups. Mice inoculated with 10^7 cells showed such a low curability that the cure rates were not affected by the regional lymphadenectomy. One can postulate that since the probability of cure of the tumor was extremely low to begin with, the immune response that might have developed was inadequate to eradicate the large number of surviving

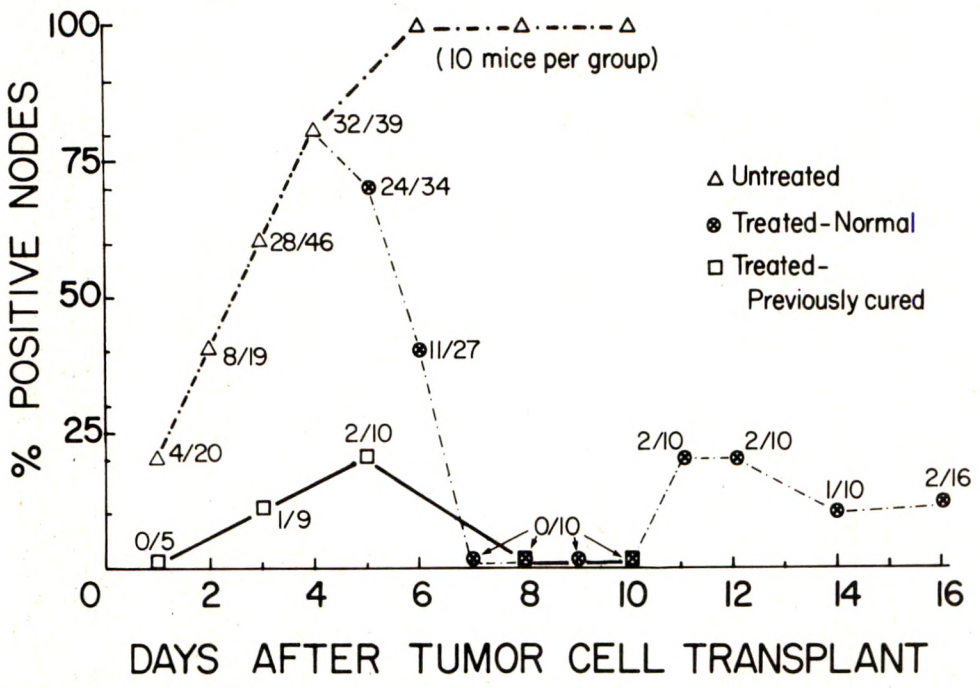

Fig. 3. Data pooled from 2 previous experiments showing the incidence of positive lymph nodes in untreated and treated mice as a function of time following the subcutaneous injection of 10^6 lymphosarcoma cells compared with previously cured mice.

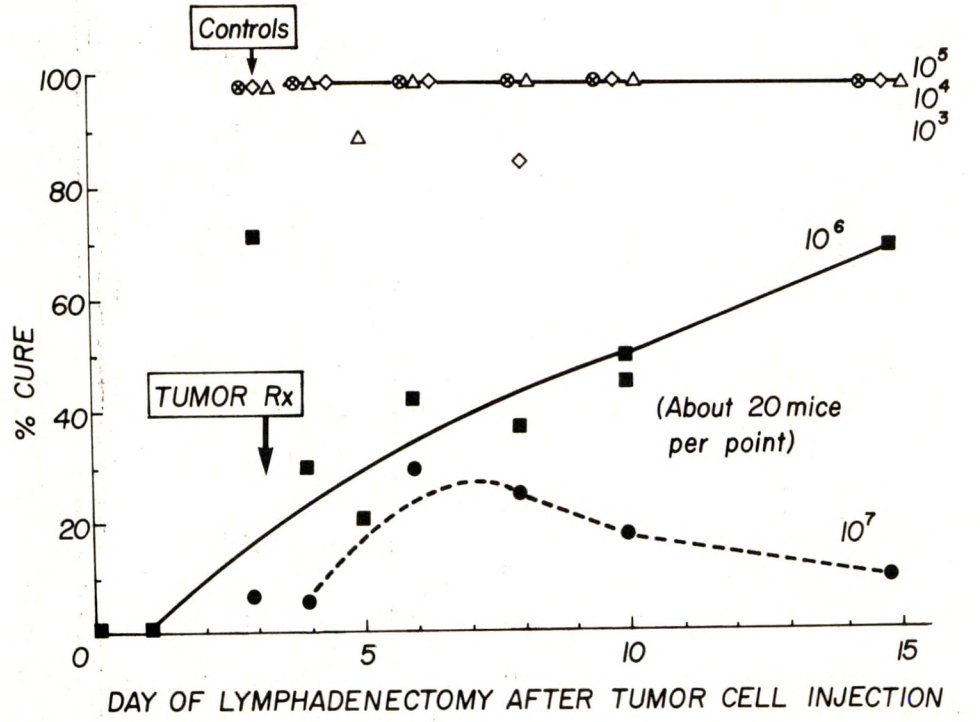

Fig. 4. Cure rates in normal mice following tumor transplantation. Mice were treated with a single dose of 4,000 rads and underwent lymphadenectomy at indicated times.

tumor cells. Previous experiments demonstrated that only 10^4–10^5 cells can be adequately handled by the animals' immune response.[28]

In this experiment, the recipient mice of dissected anterior axillary lymph node cell suspensions were matched with the irradiated donors. Initially, there was a somewhat higher percentage of positive lymph nodes in the animals injected with 10^6 and 10^7 tumor cells, followed by a decrease immediately after the irradiation of the primary tumor (Fig. 5). After Day 8, the mice found to have recurrent tumor harbored lymph nodes that became progressively more positive. In contrast, the cured mice never showed viable tumor cells in the node after the 6th day following cell injection. This elimination of tumor cells from the lymph nodes is felt to represent an early immunological response, probably initiated in the lymph nodes. In the case of mice with persistent or recurrent tumor, reseeding of the regional lymph nodes occurs by migration of tumor cells from the recurrent primary tumor, which overwhelms whatever initial immune response is present.

DISCUSSION

The regional lymph nodes, which at one time were presumed to be a mechanical barrier against dissemination of tumor cells,[8,10,39] are more recently regarded as an essential component of the host immune response, playing a major role in the initiation of immunity against a skin homograft or a tumor.[4–6,11,27,37]

Our observations in "normal" (not sensitized) or previously cured mice are strongly suggestive of a protective effect that the previous exposure to the tumor induced in the animals, and that if tumor cells migrate to the regional lymph nodes, they are effectively inactivated. Also, because of this

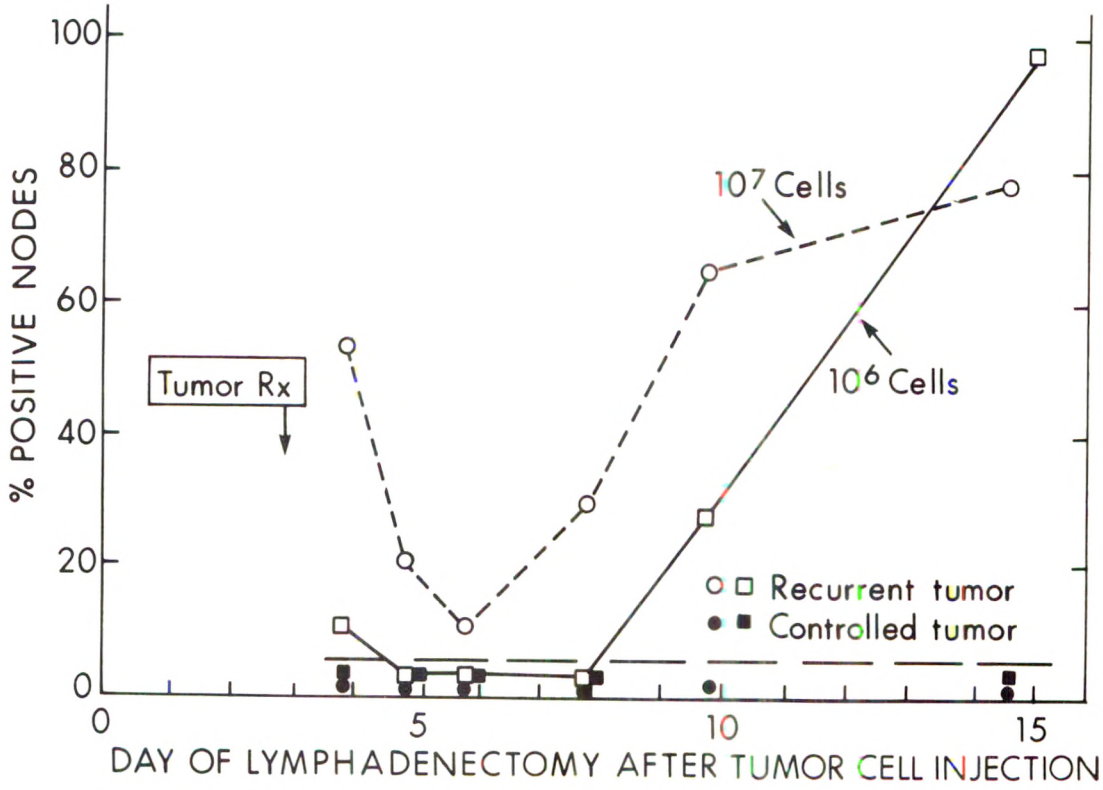

Fig. 5. Incidence of positive lymph nodes in mice locally irradiated to the primary tumor. (Mice injected with either 10^6 or 10^7 tumor cells.)

immunity, the animals are more resistant to the growth of tumor cells which survive the local irradiation. Furthermore, the fact that the regional lymphadenectomy did not significantly influence the cure rates in the previously cured mice is strongly suggestive that the immunity has become systemic and the regional lymph nodes are not required for the maintenance of immunity.

Lower cure rates were observed in these experiments in the mice not previously cured of the lymphosarcoma, when compared with previous experiments.[27] This is probably due to a "drift" in the antigenicity and histocompatibility of the tumors acquired through many weekly transfers in this strain of mice. The seemingly contradictory high incidence of axillary failures in previous experiments,[27] as opposed to a higher frequency of local recurrences in the present experiments, could be explained because of the use of tumor chunks in the former, in contrast to monodispersed cell suspensions used in this study, with an estimated higher cell inoculum transferred by the chunk transplants (10^7 cells). Regardless of the site of failure, the crucial observation is that the previously cured mice had a significantly lower tumor recurrence rate, which was not appreciably influenced by the removal of the regional lymph nodes independent of the time the procedure was done, before or after tumor transplantation.

An intact lymphatic and blood vasculature appears to be required for the development of an effective immune state.[1,4] These lymphatic vessels draining the graft carry antigenic material to the lymph nodes where the immune response is initiated (afferent path of immunological reflex arc), and later allow sensitized effector lymphocytes or antibodies to travel *via* the bloodstream to the sites of antigen deposition (efferent path of the immunological reflex arc). Stark *et al.*[38] reported that bilateral lymphadenectomy significantly enhanced the survival times of skin homografts in rabbits, suggesting that early interruption of the lymphatic pathway results in impaired immunological competence of the animal against a homograft, until other lymphatics were established to different draining lymph nodes. Crile[7] reported that the removal of the popliteal lymph nodes between days 5 and 10 following the inoculation of sarcoma 180 in Swiss mice significantly interfered with the ability of the animals to prevent tumor growth when the same sarcoma cells were reimplanted in the opposite foot at a later time. However, after the tenth day following initial tumor transplantation, immunity was no longer affected by removal of the regional lymph nodes. Fisher and Fisher[11] described the failure of mice transplanted with a mammary carcinoma to develop immunity after the removal of a growing tumor when the regional lymph nodes were excised 7 days prior to transplantation. Likewise, animals in which tumors grew for 28 days after the removal of the regional lymph nodes failed to develop the same degree of concomitant immunity present in normal controls in which the regional lymph nodes were retained.[12]

On the other hand, Gardner and Rosen[14] observed no demonstrable effect on the growth of a second tumor cell challenge using a methylcholanthrene-induced sarcoma in rats, when the regional lymph nodes were removed after the tumor had grown to the size of about 2 cm. Bard *et al.*[3] and Pilch *et al.*[30] postulated that if the regional lymphatics and lymph nodes played a major role in host resistance to a chemically-induced primary tumor transplant, an extensive regional lymphadenectomy would cause decreased resistance to tumor growth because the antigen processing afferent limb of the immune response had been interrupted. However, a series of experiments using a chemically-induced fibrosarcoma in mice in which the regional lymph nodes were removed 1 week prior to tumor challenge with 750 viable tumor cells failed to confirm the postulate. These authors demonstrated that animals subjected to amputation of the tumor-

bearing limb, but no other procedure, were highly resistant to subsequent challenge in the same chemically-induced tumor, indicating that previous contact with tumor cells had induced immunity. Hammond and Rolley,[16] using a syngeneic fibrosarcoma, concluded that the removal of the regional lymph nodes after the tumor reached a size of 1.5 cm. did not significantly affect the development of either local recurrence or distant metastases or both.

In all the experiments in which no detrimental effect was observed after regional lymphadenectomy, the lymph node removal was accomplished 3 or more weeks after tumor cell transplantation. Under these conditions, it is very likely that the immune response was already established and systemically disseminated. In contrast, in the experiments showing a detrimental effect, the lymphadenectomy was performed within a few days following tumor cell transplantation.[7,11,27] The time at which the immunity becomes systemic for different tumors probably depends on the growth rate, antigenicity of the cells and pattern of dissemination. Also, if regional lymph nodes are removed prior to tumor transplantation, collateral lymphatics may develop to new lymph nodes and a different pattern is established, other lymph nodes becoming involved in the initiation of the immune response.[20] Fisher and Fisher[12] suggested, however, that the regional lymph nodes may play a significant role in the maintenance of tumor immunity when cells have low antigenicity, such as is presumed in some spontaneous tumors.[23]

From a clinical viewpoint, it is well established that patients without lymph node metastases or less than 1 lymph node involved[29] have a significantly better prognosis than patients with multiple lymph node metastases. Furthermore, Edwards *et al.*[9] reported a regression of clinically palpable axillary lymph nodes in patients with carcinoma of the breast after treatment of the primary tumor by simple mastectomy. Although the incidence of pathologically positive lymph nodes in patients with Stage 1 carcinoma of the breast is about 35 per cent, patients treated for this lesion with a simple mastectomy, without lymph node dissection, show less than 10 per cent clinical incidence of lymph node metastases.[6]

Whereas it is common practice to surgically remove or irradiate regional lymph nodes clinically involved by metastatic tumor, a more controversial issue is that of prophylactic removal or irradiation of regional lymph nodes not grossly invaded by cancer. Increased survival has been reported in patients with head and neck tumors,[35] melanoma,[15] and carcinoma of the vulva,[13] when "prophylactic" or "elective" lymph node dissections were performed. However, others, such as Crile,[6] Fisher and Fisher,[11] and Prehn[31] have proposed that this lymph node removal may result in decreased cure rates because of impairment of the immunological response of the host. Reed and Miller,[32] and Staley and Herzon[37] remarked that available data fail to support the contention that elective neck dissection improves the survival of patients with laryngeal carcinoma. Similar observations were made by Sandeman[33] in cutaneous melanoma.

CONCLUSION

Experiments reported previously, as well as those described herein, strongly support the concept that the interference with the immune response produced by a regional lymphadenectomy occurs only during the initial phase of the immune response following antigenic stimulation, before immunity becomes systemic. Theoretically, by the time a tumor becomes clinically apparent, tumor cells have reached the regional lymph nodes and an adequate immune response has developed. Prophylactic dissection of these lymph nodes should not interfere with tumor control by the usual therapeutic methods. However, if the body has not recognized the tumor antigens, a regional lymphadenectomy may produce appreciably less therapeutic results be-

cause of interference with the immune response of the host.

A greater degree of understanding of some important issues is necessary to further define the immuno-reactivity of the lymph nodes. For example, through laboratory and clinical investigation, we should further explore the mechanisms involving the recognition and processing of tumor antigens, the evolution of the development and maintenance of the immune response, and the effects that surgical removal of uninvolved regional lymph nodes may have on the cure of cancer patients.

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ATTENUATION OF MONOENERGETIC GAMMA RAYS IN TISSUES*

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WHILE linear attenuation coefficients for x or gamma radiations have been tabulated for a wide variety of substances, human tissues have been an unfortunate exception. For making reasonable estimations, values of the linear attenuation coefficient (μ) have been calculated and tabulated for "striated muscle" and "compact femur bone" using their chemical compositions.[3,6] For even cruder calculations it has been sufficient to assume that water and soft tissue are the same.

Recently, a new diagnostic procedure has been introduced that can compute and image the attenuation coefficients of an array of elements on a tomographic slice of an organ.[5] It has been claimed that with this device (known generally as a computer assisted tomographic scanner), differences on the order of 1 per cent in μ within an organ can be visualized. This method has also been used to estimate the attenuation coefficients of tissues within the brain. It is therefore of greater interest now to perform an independent measurement of such μ's, especially to detect any differences that may exist between normal and diseased tissues. This will serve: (a) as a check on the new scanner mentioned above; and (b) to define the limits of accuracy to which sensitive imaging systems can be refined.

We determined the linear attenuation coefficients of human tissues for photon energies ranging from 27 to 662 kev. This covered all energies of interest in diagnostic radiology and also provided the relative dependence of various tissues on average atomic number. For example, the photoelectric effect, which depends strongly on atomic number, accounted for about 50 per cent of the attenuation at 27 kev. but was negligible at 100 kev. or more. Specific gravity determinations were also made in order to possibly account for any as yet unobserved tissue variations at high energies. Such measurements are also of value in ultrasound.[4]

Measurements were made for a variety of tissues and the results are tabulated in this paper. It should be pointed out that it is the attenuation coefficients, and not absorption coefficients, which have been listed, and that the former are of greater relevance when evaluating diagnostic methods.

EXPERIMENT

The 5 radioisotopes shown in Table 1 were used. Their radiations were either monoenergetic or sufficiently so for our purpose. In the case of I^{125} a filter of tin, which has a K-absorption edge at 29.2 kev., was used to reduce the components above that energy. The radiation from Co^{57} was assumed to be monoenergetic, since the component at 136 kev. was much weaker than that at 122 kev. and could not be distinguished from it. Also, μ for tissues was found to vary slowly at these energies.

TABLE I

A LISTING OF RADIOISOTOPES USED

Radioisotope	Photon Energies in kev.
I^{125}	27.5 (74%), 27.2 (38%), 31.0 (20%), 31.7 (4%), 35.4 (7%)
Am^{241}	60 (36%)
Co^{57}	122 (85%), 136 (11%)
Hg^{203}	279 (81%)
Cs^{137}	662 (85%)

* From the Department of Radiology, Case Western Reserve University, Cleveland, Ohio.
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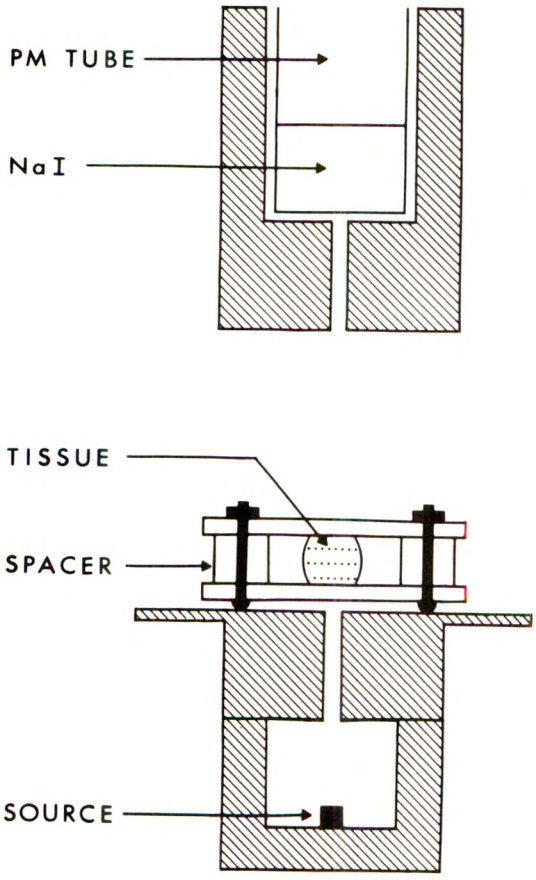

Fig. 1. Schematic illustration of apparatus used.

The Am^{241} and Cs^{137} isotopes were solids encapsulated within sealed buttons of small diameter, while the other 3 were in solution form contained in stoppered V-vials. Thus all sources were of sufficiently small size and ensured good geometry. Activities were on the order of 2 to 5 millicuries.

The apparatus is shown in Figure 1. The radionuclide was placed at the bottom of a lead container fitted with a lead cap. A beam of gamma radiation emerged from a hole of $\frac{1}{4}$ inch diameter in the cap.

The tissue samples were held between 2 plastic plates screwed together. Carefully machined spacers were used to separate the plates by well-defined distances. The tissue was cut so as to almost equal the thickness of the spacers, and when in place it was slightly compressed to attain the dimension of the spacers. In a preliminary experiment with a human liver it was found that compressing the tissue from a thickness of 2.1 to 2.0 cm. produced no observable change. It was assumed, thereafter, that nearly all tissues were sufficiently elastic and that any error due to compressing it was well within the limits of accuracy of the experiment.

Liquids such as blood were either poured into plastic cups and their heights measured with the aid of a micrometer, or held in the container illustrated in Figure 2.

The detector was a 2 inch×2 inch NaI (Tl) crystal well-enclosed by lead shielding in which a $\frac{1}{4}$ inch hole was drilled and aligned with the gamma-ray beam. Following the crystal were a photomultiplier tube and a standard counting circuit with a single-channel analyzer.

Counts were noted with and without the sample in the gamma-ray beam, and corrections were applied for background and the resolving time of the amplifier. The attenuation coefficient was then calculated using the exponential law of attenuation. The measurement was repeated at least 10 times, and a mean value of μ obtained. The standard deviation of the mean was calculated and expressed as a percentage of μ, and this figure was used as a measure of accuracy of our results. It varied from sample to sample and with the energy of the gamma rays, with the highest figures being 0.4 per cent, 0.9 per cent and 1.6 per cent at 27, 60 and 662 kev., respectively. However, for most tissue samples, and at

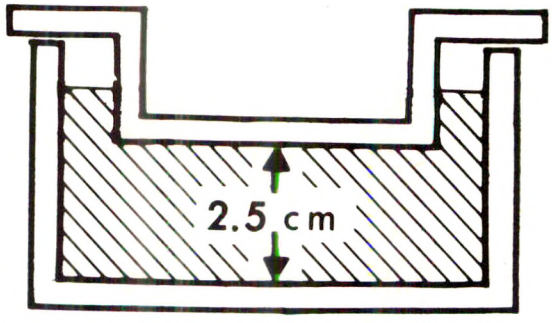

Fig. 2. Schematic illustration of plastic container for ensuring fixed distance of transmission for liquids. Enough liquid is poured into it so as to reach and flow around the upper horizontal sheet of plastic.

TABLE II

LINEAR ATTENUATION COEFFICIENTS IN CM.$^{-1}$ OF ANIMAL TISSUES

Tissue	Photon Energy in kev.					Sp. Gr.
	27	60	122	279	662	
1. Steer Muscle	.446	.219	.166	.128	.0905	1.06
2. Steer Fat	.304	.188	.150	.117	.0812	0.94
3. Steer Brain	.449	.219	.163	.122	.0871	1.03
4. Steer Brain	.442	.215	.165	.125	.0895	1.03
5. Steer Liver	.470	.225	.171	.129	.0905	1.08
6. Steer Liver	.459	.222	.170	.128	.0914	1.08
7. Steer Pancreas	.434	.217	.164	.125	.0871	1.03
8. Steer Kidney	.454	.218	.165	.127	.0897	1.05
9. Steer Lung	.118–.187	.066–.092	.052–.064	.042–.056	.033–.043	.46–.73
10. Egg White	.451	.219	.164	.126	.0886	1.04
11. Egg Yolk	.426	.215	.162	.123	.0881	1.04

Sp. Gr. = specific gravity.

60 kev., the figure was about 0.5 per cent.

Wherever possible, the specific gravity of a tissue specimen was measured with a Jolly balance. If the specimen was small, it was used for measuring both μ and the specific gravity in that order. If it was large, small pieces were cut away for the specific gravity measurement alone.

RESULTS

The results for a large number of tissues are displayed in Tables II–VIII. Measurements on a tissue specimen were usually made within a day of obtaining it. If several specimens were obtained together, observations were made only for the more important gamma-ray energies so as to save time.

If both normal and cancerous tissues were present in a specimen, measurements were made on adjacent sections that were either all normal or all tumor. Otherwise, if the specimen was large enough, measurements were made on different sections and a mean result calculated. No averaging over different tissue specimens was made.

TABLE III

LINEAR ATTENUATION COEFFICIENTS IN CM.$^{-1}$ OF FLUIDS

Fluid	Photon Energy in kev.					Sp. Gr.
	27	60	122	279	662	
1. Water	.421	.205	.159	.122	.0860	1.00
2. CSF	.448	.213	.160	.122	.0854	1.00
3. CSF	.446	.208	.161	—	.0868	—
4. CSF	—	.212	.159	—	.0867	—
5. Blood	.457	.217	.170	.130	.0909	—
6. Blood	.463	.222	.168	.127	.0911	1.04
7. Blood	.454	—	.168	—	.0896	1.03
8. Blood	.455	.217	.169	.128	.0910	1.03
9. Blood	.459	.214	.168	—	.0909	—
10. Blood	.458	.215	—	—	—	—
11. Evaporated Blood	.477	.223	—	—	.0938	1.09

Sp. Gr. = specific gravity; CSF = cerebrospinal fluid.

TABLE IV

LINEAR ATTENUATION COEFFICIENTS IN CM.$^{-1}$ OF NORMAL HUMAN TISSUES

Tissue	Photon Energy in kev.					Sp. Gr.
	27	60	122	279	662	
1. Heart Muscle	.448	.212	.165	—	.0878	1.04
2. Subcutaneous Fat	.328	.190	.153	.120	.0825	0.93
3. Liver	.441	.221	.165	.126	.0900	1.05
4. Pancreas	.436	.215	.165	.126	.0896	1.02
5. Spleen	.458	.216	.168	.127	.0896	1.06
6. Breast	.317	.189	.152	.111	.0812	0.97

Sp. Gr. = specific gravity.

The first experiments were carried out with a variety of animal tissues obtained from a slaughterhouse, and the results are in Table II. One of the points of interest is the wide range of values obtained for different samples taken from a lung of a freshly slaughtered steer. The range is due to the varying number and sizes of air-filled bronchi in the samples.

Table III shows the results of measurements on different fluids. The samples of cerebrospinal fluid were obtained fresh from patients about to undergo myelographic procedures. Among the blood samples, the first was fresh and was heparinized to prevent clotting, while the rest were obtained from a blood bank and had been citrated. The last set of measurements was made on blood that had been evaporated rapidly under vacuum to form a dense fluid, such as might be found in a hematoma. As expected, the denser fluid had higher values of μ than ordinary blood. This has been corroborated by others.[8]

TABLE V

LINEAR ATTENUATION COEFFICIENTS IN CM.$^{-1}$ OF DIFFERENT SECTIONS FROM A HUMAN BRAIN

Tissue Location	Photon Energy in kev.	
	60	662
Thalamus	.214	.0899
Pons	.214	.0892
Cerebellum	.214	.0893
Cerebrum—Gray	.213	.0884
Cerebrum—White	.215	.0882

Table IV indicates values obtained for a variety of normal tissues. Each value was obtained from measurements made at only one place in the corresponding organ, and so it should not be taken to uniquely characterize the organ as a whole. Some variation (about 1 per cent) was observed from place to place within a large organ, as shown in Tables V and VI.

Table VII contains the results on a number of brain tissues, of which the first 2 were obtained from autopsies and the rest from surgery. The first one was fixed in formalin. Two points may be noted. First, fixing in formalin lowers the absolute values of μ, presumably because the solution has a lower density and mean atomic number than brain tissue. Second, the first 3 sets of results, including those for the fixed specimen, show direct comparisons between normal and tumor tissues, and no difference in their attenuation coefficients can be detected that exceeds experimental error. Table VIII lists such comparisons for other organs.

DISCUSSION

Our results have 2 limitations: (a) a mean accuracy which is about $\frac{1}{2}$ per cent at 60 kev., which is the approximate energy at which the computer assisted diagnostic examinations are made; and (b) the fact that our tissue samples have not been *in vivo*. In the process of excision and cutting to our required dimensions, the tissue samples may have lost some body fluids and thereby changed in attenuation properties. No

Table VI

LINEAR ATTENUATION COEFFICIENTS IN CM.$^{-1}$ OF DIFFERENT SECTIONS FROM TWO HUMAN LIVERS

Tissue	Photon Energy in kev.					Sp. Gr.
	27	60	122	279	662	
I. i)	.456	—	—	—	.0915	1.07
ii)	.461	—	—	—	.0917	1.07
iii)	.458	—	—	—	.0912	1.07
iv)	.460	—	—	—	.0914	1.07
II. i)	.461	—	—	—	.0922	1.07
ii)	.456	—	—	—	.0918	1.07
iii)	.459	—	—	—	.0916	1.07
iv)	.460	—	—	—	.0908	1.07
v)*	.453	.211	.165	.125	.0887	1.03

* These measurements were made on blood that was exuded by the liver within a day of excision.
Sp. Gr. = specific gravity.

method exists yet of measuring this effect, and we have chosen to neglect it for the time being. In any case, such an effect should be the same in contiguous areas, and so comparisons between adjacent sections should still be valid.

Within these limitations, certain broad conclusions can be drawn:

1. Considerable variations exist in samples of tissue from one person to another,

Table VII

LINEAR ATTENUATION COEFFICIENTS IN CM.$^{-1}$ OF HUMAN BRAIN TISSUES

Tissue	Photon Energy in kev.					Sp. Gr.
	27	60	122	279	662	
1. (Fixed Specimen)						
Normal Cerebrum	.424	.201	.161	.123	.0875	1.04
Glioblastoma						
—pons	.422	—	—	—	.0877	1.04
—cerebrum	.426	—	—	—	.0854	1.05
2. Normal	.451	.218	.171	.128	.0907	1.03
Glioblastoma	.454	.219	.170	.127	.0911	—
Necrotic Center	.456	—	—	—	.0907	1.03
3. Normal	—	.218	—	—	—	—
Low Grade Astrocytoma	—	.216	—	—	—	—
4. Astrocytoma Grade III						
—core	.453	.211	.164	.124	—	—
—fringe	.448	.208	.161	.126	—	—
5. Astrocytoma Grade II	—	.212	.161	.123	—	—
6. Frontal Parietal Tumor	.446	.214	.171	—	—	—
7. Gamesticitic Astrocytoma Grade III						
i)	.439	.219	—	—	.0887	—
ii)	.441	.220	—	—	.0901	—
8. Meningioma	.460	.214	—	—	.0901	1.05
9. Cerebellar Tumor	.454	.218	—	—	.0882	1.05

Sp. Gr. = specific gravity.

TABLE VIII

LINEAR ATTENUATION COEFFICIENTS IN CM.$^{-1}$ OF NORMAL AND ABNORMAL TISSUES

Tissue	Photon Energy in kev.					Sp. Gr.
	27	60	122	279	662	
1. Liver—Normal	.455	.220	.169	.128	.0930	1.07
—Hepatoma	.449	.219	.165	.128	—	1.07
2. Liver—Normal	.447	.219	.168	.128	.0907	1.06
—Adenocarcinoma Metastasis	.445	.215	.165	.125	.0892	1.05
3. Liver—Normal	.466	.216	—	—	.0906	1.06
—Breast Tumor Metastasis	.451	.212	—	—	.0891	1.04
4. Liver—Normal	.461	.208	.172	—	—	1.05
Liver—Reticulum Cell Sarcoma	.462	.209	.174	—	—	1.05
5. Pancreas—Normal	.439	.214	—	.127	—	1.03
—Tumor	.436	.211	.168	.125	.0888	1.03
6. Lung (fixed)						
—Normal	.339	.167	.123	.091	.0658	0.76
—Tumor	.461	.221	.169	.128	.0896	1.06

Sp. Gr. = specific gravity.

and possibly lesser variations (up to 1 per cent) within the same organ from the same person.

2. In general, differences in μ between normal and cancerous tissues lie within 1 per cent, which is also the observed range of variation within normal tissues. Where a greater difference exists, there is also a marked difference in specific gravity.

3. The mean atomic number is the same for all tissues, except fat and breast tissue.

The implications regarding computerized tomographic scanning can now be examined. The efficacy of such a technique in tumor detection depends on the variation in linear attenuation coefficients between neighboring regions of tissue. This may be due to (a) a change in gross physical density such as may occur in cystic formations, or (b) a change in vascularity in some tumors. The latter seems quite likely, since many tumors have been better visualized after the introduction of iodinated contrast medium.[1,7] Concentrations as high as 4 mg. iodine per ml. blood have been reported,[2] and from Figure 3 it can be seen that this would lead to about 14 per cent increase in the μ of blood. The μ of tissue will increase by about 1.4 per cent, if blood is assumed to constitute one-tenth of brain tissue, and variations in this proportion due to vascularity differences may be enhanced. For such lesions, their detectability without iodination hinges entirely on the relative

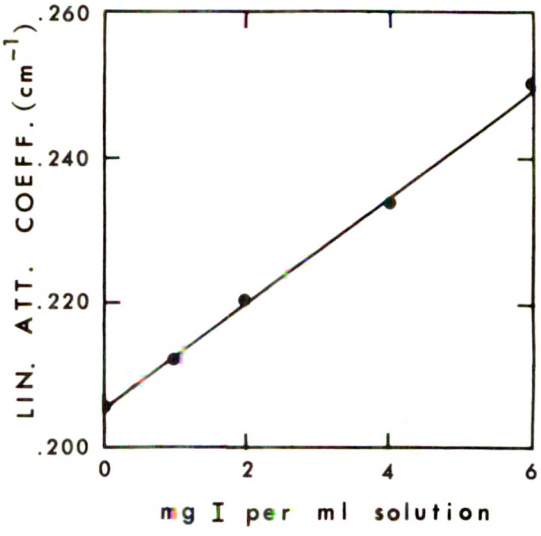

FIG. 3. Linear attenuation coefficient of water-iodine solution *versus* concentration of iodine. Data were obtained by measuring the coefficient at 60 kev. for different dilutions of Renografin 60.

values of μ of blood and soft tissue, which may differ by anywhere from 0 to 1 per cent. The significance of our results is that it is not possible to characterize a particular kind of tumor by (a) a specific value of μ, or even (b) the difference between the μ's of a tumor and its surroundings.

Clearly, further work needs to be done in measuring attenuation coefficients of tissues, and one area of interest will be the possible change in the coefficients when a tissue loses viability. It is hoped that results on this will be forthcoming soon.

SUMMARY

Using gamma-emitting radioisotopes and a crystal spectrometer we measured linear attenuation coefficients for a variety of tissues at photon energies of 27, 60, 122, 279, and 662 kev. The fractional standard deviations of the observed values varied with tissue thickness, but were about 0.5 per cent in most of the cases. Specific gravities of the tissue samples were measured wherever feasible. Our results indicate that the attenuation coefficients of different parts of the same organ may vary by up to 1 per cent. For most of the tumors investigated, no significant differences were found between the attenuation coefficients of cancerous tissues and their normal parenchyma.

Some attenuation coefficients were measured for a few of the materials commonly used as phantom materials. The results are presented in Table IX.

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TABLE IX

LINEAR ATTENUATION COEFFICIENTS IN CM.$^{-1}$ OF TISSUE-LIKE MATERIALS

Material	Photon Energy in kev.		Sp. Gr.
	60	662	
1. Water	.205	.0860	1.00
2. Mix D	.205	.0859	0.97
3. Polystyrene	.196	.0885	1.05
4. Plexiglass	.228	.1006	1.19

Sp. Gr. = specific gravity.

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THE USE OF SILICONE COMPENSATORS IN RADIOTHERAPY*

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THE radiologic uses of *in vivo* silastic molds, both in diagnosis and therapeutically, as a preliminary intracavitary cast for a radioactive materials stent or carrier, have been documented previously in the surgery and radiotherapy literature.[1–3] In addition, the cooperative efforts of radiotherapists, radiation physicists and prosthodontists have been appreciated for quite some time, especially in the management of patients with head and neck cancer. This multidisciplined approach has resulted in better patient care through improved techniques in the delivery of treatment as well as in the pre- and postoperative care of the patient.

We wish to present a new technique for correcting the nonuniform distribution of ionizing radiation in certain clinical situations where it is desirable to employ external beam megavoltage radiotherapy.

FIG. 1. Radiation portals showing distorted topography and large "dead space."

BACKGROUND

The therapeutic effect of ionizing radiation on a patient is largely determined by the magnitude of the absorbed dose and its uniform distribution in both space and time. Radiation dosimetry to assess the magnitude and distribution of a dose, within a patient, is frequently based upon the assumed distribution of radiation, usually with the radiation beam being directed at right angles to the plane surface of a homogenous tissue equivalent medium (water phantom). It must be recognized, however, that the surface of the patient is neither plane nor homogenous and dosimetry based on such assumption is only approximate to the dose within the patient. To eliminate the problem in certain patients, "tissue-equivalent" silicone can be utilized to fill a dead space (non-displaced compensator) or displace or improve the plane of the tissue in question.

REPORT OF CASES

CASE 1. A 50 year old male presented with a squamous cell carcinoma of the right antrum involving the inferior wall of the orbit. Treatment consisted of a radical antrectomy and orbital exenteration. This was followed by a therapeutic dose of radiation consisting of 6,100 rads (100 per cent isodose volume) over a 46 day period (32 fractions—NSD 1,740 rets) employing a 4 MV linear accelerator.

Because of the orbital exenteration, the topography of the radiation portal was extremely distorted (Fig. 1). The non-planar surface with a large air-gap would result in distor-

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tion of normal isodose curves, making it extremely difficult to approximate the magnitude of radiation or its distribution in the treated volume. To circumvent this problem silicone* was utilized to fill the dead space during treatment.

In the dental laboratory an impression of the area was made with irreversible hydrocolloid. A stone cast was made and all severe undercuts blocked out with dental stone. The cast was then lubricated and the silicone prepared and poured directly into the area (Fig. 2). When set, the silicone was removed, trimmed, and sent to radiotherapy for use (Fig. 3; and 4). The clinical fit was excellent and the compensator was inserted for daily treatments utilizing a topical Polymixin ointment as a lubricant.

The silicone in conjunction with 45 degree wedge filters 90 degrees apart provided accurate magnitude of dose as well as uniform distribution of dose within the volume of interest. TLD dosimeters of lithium fluoride were easily placed within the silicone to determine the agreement of daily dose magnitude with the treatment plan. Excellent agreement was noted. The computer-generated dosimetry plan demonstrates the isodose distribution (Fig. 5). For very large depths (*i.e.*, greater than 8–10 cm. compensation) the silicone is not tissue-equivalent, there being about 10 per cent greater absorption than in water. For the thickness described in this paper, the material is "tissue-equivalent" as verified by thermoluminescent dosimetry (±3 per cent).

* Silastic 382, Dow Corning, Midland, Michigan.

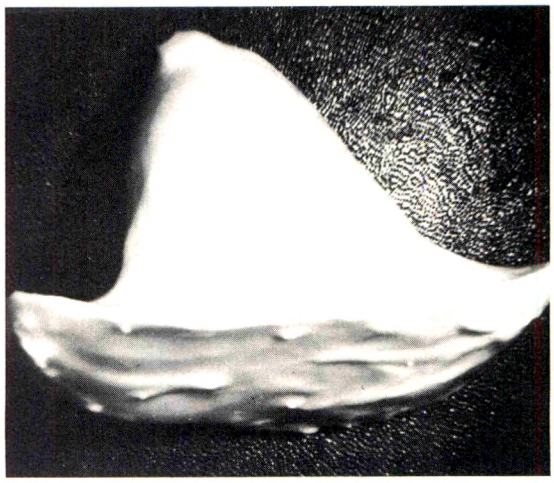

Fig. 3. Completed silicone bolus as sent to radiotherapy.

Case II. An 85 year old male presented with a large lesion of the pinna of the left ear (Fig. 6). It was diagnosed as a moderately well-differentiated squamous cell carcinoma with involvement of the entire helix extending posteriorly into the scalp behind the base of the ear. There was no lymphadenopathy. We elected to treat the patient with megavoltage radiotherapy employing a 4 MV linear accelerator.

The maximum dose for a 4 MV x-ray field

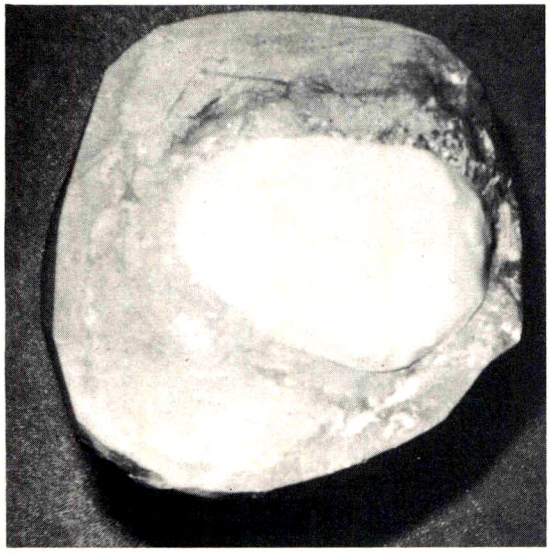

Fig. 2. Set silicone in mold.

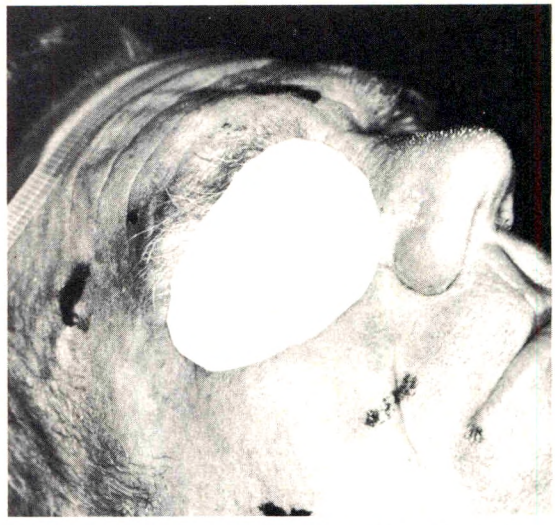

Fig. 4. Silicone bolus in place for treatment.

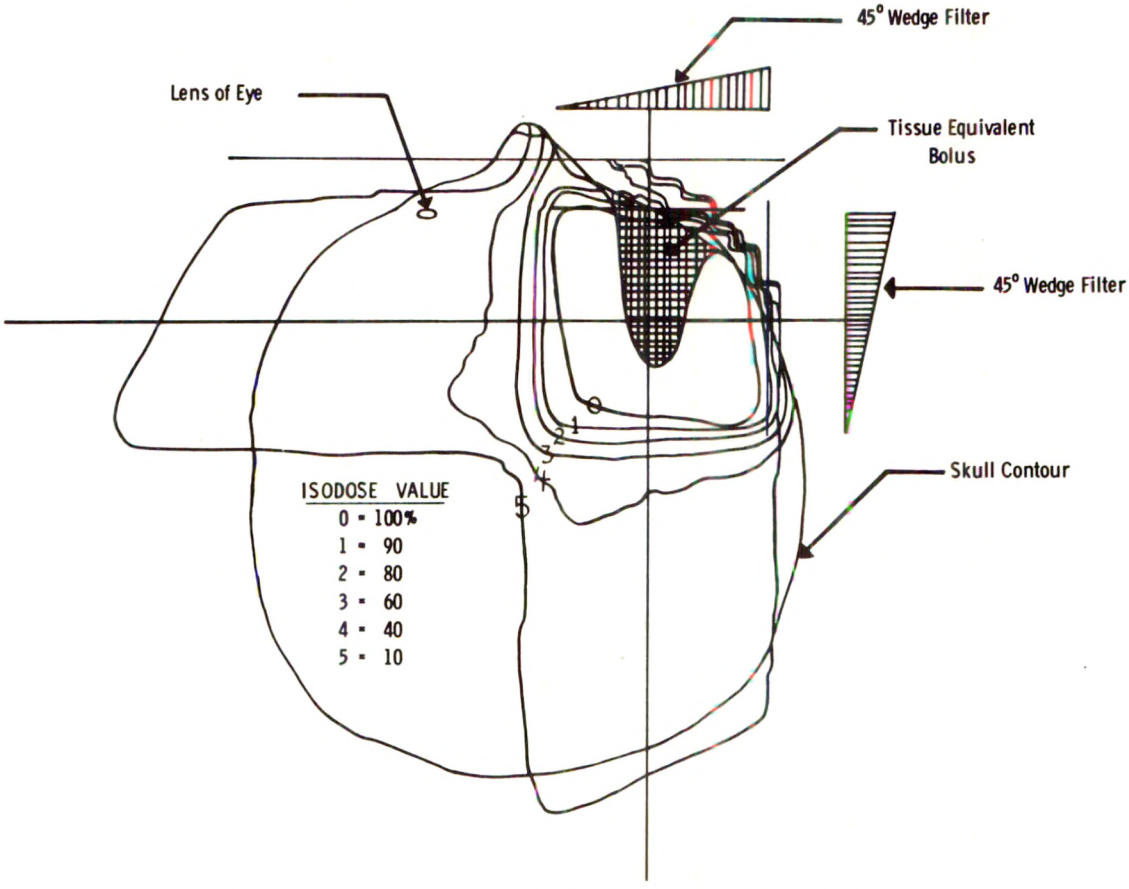

Fig. 5. Computer generated dosimetry plan showing volume to be treated within the area of greatest concentration.

occurs at a depth which equals the maximum range of the secondary electrons released in the absorbing medium. In other words, tissue approximately 12 mm. in thickness is required to bring the surface dose to maximum for a 4 MV x-ray field. In the treatment of the entire ear and a portion of the scalp, the maximum dose was required to occur at the surface of the ear as well as at depth, within the scalp and base of the ear.

In order to accomplish this, a build-up of approximately 15 mm. was needed. This was accomplished in silicone. An impression was made, poured in dental stone, and a cast recovered. On the cast, the build-up was fabricated in wax and invested in a two-part model and the silicone processed. The build-up was recovered in one piece, cleansed of investing stone and cut in two with a scalpel to facilitate placement on the patient (Fig. 7; and 8). There was no need to index the halves as they fit well

Fig. 6. Squamous cell carcinoma of pinna of ear extending to retroauricular tissues.

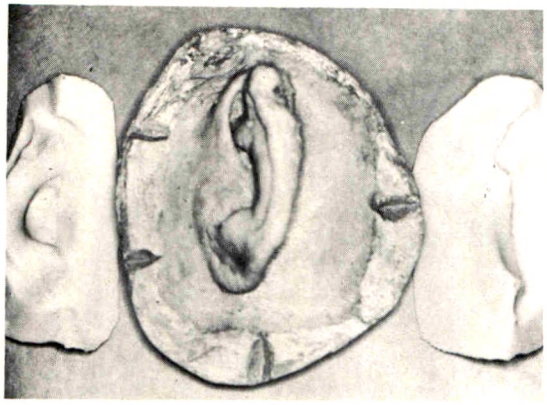

Fig. 7. Silicone "build-up" after sectioning and master model.

together (Fig. 9). Again a topical antibiotic was utilized with each application of the mold. Tape was used to hold the build-up material as well as establishing a right angle to be utilized in conjunction with 45 degree wedge filters. This provided a very acceptable magnitude and distribution of the dose. The "build-up" allowed the radiation beams to be directed at right angles to the ear with a 90 degree angle separation between the beams. This is an optimal arrangement for 45 degree wedge filters. The TLD dosimeters demonstrated that the actual daily dose was in excellent agreement with the treatment plan. The computer-generated dosimetry plan demonstrates the isodose distribution (Fig. 11). The patient received 6,010 rads in 36 days (27 fractions—NSD 1,830 rets).

Fig. 8. Half of "build-up" on model to show method of placement.

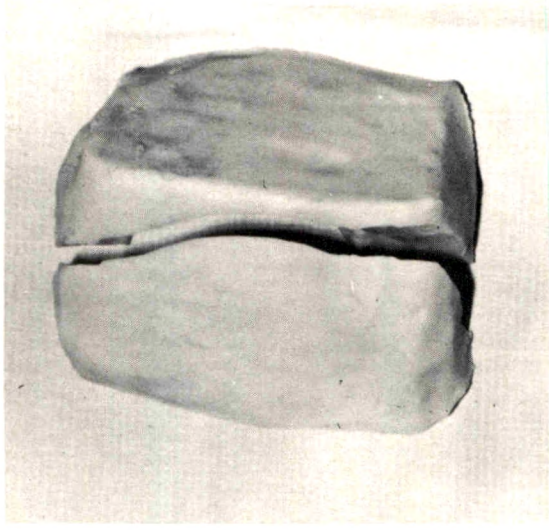

Fig. 9. Sectioned "build-up" molds.

CONCLUSIONS AND SUMMARY

In the 2 patient histories presented, the usefulness of silicone has been demonstrated. By utilizing silicone, no special materials are necessary. Those which are already present in the dental office are more than adequate. The silicone will not distort over the treatment period and can

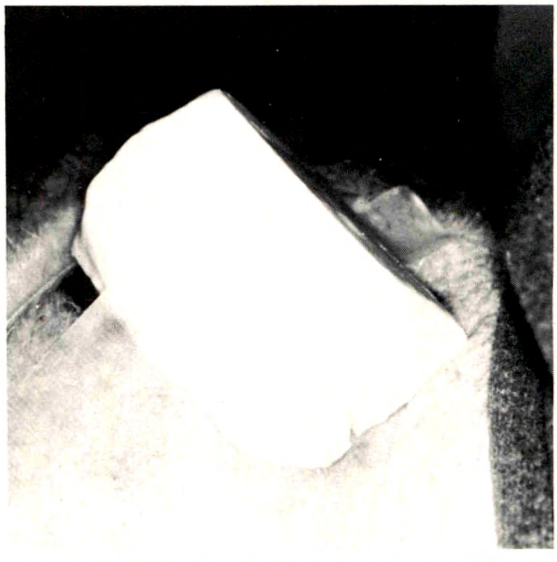

Fig. 10. Silicone "build-up" held in place with tape during treatment. Note planar entry surfaces for x-ray beams.

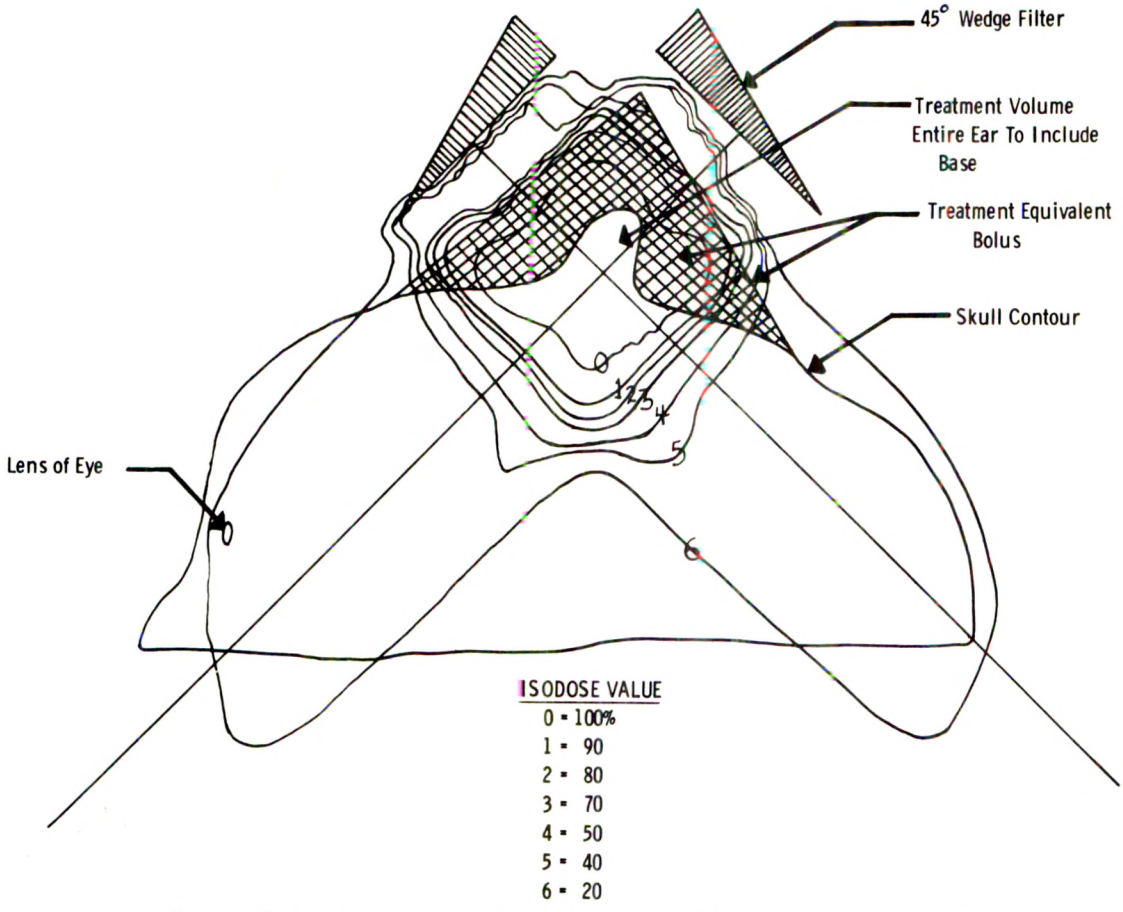

FIG. 11. Computer generated dosimetry plan showing volume to be treated within the area of greatest concentration.

be repositioned accurately to ensure uniformity of the dose. It is also easily cleaned and stored for daily use. It can be used to improve the plane of the surface tissue and provide "build-up" as well as to fill "dead space" which helps assure accurate assessment of the magnitude and distribution of the desired dose.

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Manager of the Annual Meeting: G. A. Kling, Harper Hosp., Detroit, Mich. 48201; Consultant, James C. Cook, Detroit, Mich.

Editor Emeritus: T. Leucutia, 401 Professional Building, Detroit, Mich. 48201; *Acting Editor:* E. Frederick Lang, Detroit, Mich.

Representative on the Board of Chancellors and Council of the ACR: W. B. Seaman.

Seventy-sixth Annual Meeting: Marriott Hotel, Atlanta, Ga., Sept. 30–Oct. 3, 1975.

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Representative on the Board of Chancellors of the American College of Radiology: Juan A. del Regato, Colorado Springs, Colo.

Fifty-seventh Annual Meeting: Americana Hotel, San Juan, Puerto Rico, May 4–9, 1975.

EDITORIALS

NCRP STANDING ORDER SYSTEMS

ABOUT 4 years ago, the National Council on Radiation Protection and Measurements (NCRP) initiated a mechanism which simplifies the process of keeping up-to-date with NCRP recommendations. This was the creation of the Standing Order List for NCRP Publications. It is quite possible that many of the readers of the AMERICAN JOURNAL OF ROENTGENOLOGY, RADIUM THERAPY AND NUCLEAR MEDICINE are not familiar with this simple means of assuring that their collection of NCRP reports is kept up-to-date. As a result, it seems appropriate to call the reader's attention to the NCRP's system.

At the time the standing order system was established, the NCRP reviewed sales records for NCRP reports and established that many individuals and organizations wish to maintain a complete set of NCRP documents. Prior to establishment of the standing order system, this required that users place an order for each new NCRP report as it was published. This meant that one had to be alert for announcements of new publications and, in the normal course of things, one inevitably missed a new report and soon developed gaps in the collection. The Standing Order List established by the NCRP, however, allows individuals and organizations to place their name on the list and thereby automatically receive each new NCRP report as it is published. Individuals and organizations on the Standing Order List are sent each new report as it is published, and are then invoiced for the report sent pursuant to their standing order. Presumably, there are very few people involved in radiation work who should not maintain a complete set of NCRP Publications and the Standing Order List provides a ready mechanism for meeting this need.

To add your name to the Standing Order List simply direct your request to NCRP Publications.

Since you may wish to fill in the gaps in your collection at the time you place your standing order, a list of the currently extant reports of the NCRP is appended below.

NCRP Report No.	Title
8	Control and Removal of Radioactive Contamination in Laboratories
9	Recommendations for Waste Disposal of Phosphorus 32 and Iodine 131 for Medical Users
10	Radiological Monitoring Methods and Instruments
12	Recommendations for the Disposal of Carbon 14 Wastes
14	Protection Against Betatron-Synchrotron Radiations Up to 100 Million Electron Volts
16	Radioactive Waste Disposal in the Ocean
22	Maximum Permissible Body Burdens and Maximum Permissible Concentrations of Radionuclides in Air and in Water for Occupational Exposure
23	Measurement of Neutron Flux and Spectra for Physical and Biological Applications
25	Measurement of Absorbed Dose of Neutrons and of Mixtures of Neutrons and Gamma Rays
27	Stopping Powers for Use with Cavity Chambers
28	A Manual of Radioactivity Procedures
30	Safe Handling of Radioactive Materials
31	Shielding for High-Energy Electron Accelerator Installations
32	Radiation Protection in Educational Institutions
33	Medical X-Ray and Gamma-Ray Protection for Energies Up to 10 MeV—Equipment Design and Use
34	Medical X-Ray and Gamma-Ray Protection for Energies Up to 10 MeV—

NCRP Report No.	Title
	Structural Shielding Design and Evaluation
35	Dental X-Ray Protection
36	Radiation Protection in Veterinary Medicine
37	Precautions in the Management of Patients Who Have Received Therapeutic Amounts of Radionuclides
38	Protection Against Neutron Radiation
39	Basic Radiation Protection Criteria
40	Protection Against Radiation From Brachytherapy Sources
41	Specification of Gamma-Ray Brachytherapy Sources
42	Radiological Factors Affecting Decision-Making in a Nuclear Attack

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The Johns Hopkins University
School of Medicine
Vice President for Health Divisions

and

Eugene L. Saenger, M.D.
NCRP Representative of the American Roentgen Ray Society

NCRP REPORT NO. 42

RADIOLOGICAL FACTORS AFFECTING DECISION-MAKING IN A NUCLEAR ATTACK

Issued November 15, 1974

IN 1954 the Federal Civil Defense Administration (FCDA) informally requested that the National Committee on Radiation Protection and Measurements (NCRP) provide information as to the radiation exposures that might be acceptable in several categories of civil defense work in emergency conditions. In response to this request an *ad hoc* group appointed by the NCRP furnished the FCDA with the information then available.

In response to a formal request to undertake a broader study of the problems in emergency exposures that might result from nuclear weapon attack, the NCRP, in 1955, established a subcommittee for this purpose. Attention was focused on the extent to which whole-body exposure to gamma radiation resulted in: (a) early injury; (b) impaired capacity to work; (c) reduced fertility; (d) late somatic (body) effects such as leukemia, cancer, cataracts, and life shortening; and (e) genetic injury. Initially, the subcommittee examined in detail the problem of stipulating values for permissible dose for selected personnel engaged in tasks of varying priority during the post-attack period. However, it became apparent that this approach—however commendable in the case of a radiation accident in peacetime—was not realistic in a nuclear war. The subcommittee became convinced that the primary problem was national survival; *i.e.*, the question of how much radiation a society could survive, rather than how much is individually acceptable or permissible. The subcommittee shared with many others the enormous psychological difficulty of coming to grips with the concept of nuclear war as a disaster that may be experienced and from which there may be recovery. After considerable debate, the subcommittee decided to prepare an information base for the decision-making that might be required in civil defense operations during and after a nuclear attack. The result was NCRP Report No. 29, Exposure to Radiation in an Emergency, which was published in 1961.

NCRP Report No. 29 dealt with radiation emergencies in general and included some aspects not necessarily associated with nuclear war. It has been widely distributed and many of its recommendations have been incorporated into the civil defense programs of the United States and other countries. New information developed since the publication of that Report has stimulated its revision, however. In 1968 the NCRP reactivated the subcommittee that had been responsible for the drafting of Report No. 29, as Scientific Committee 14, to revise Report No. 29. The intent was to produce a new report on radiological problems associated with nuclear attack, using data from accidental human radiation exposures and contemporary experimental radiobiological information to evaluate how fractionation and protraction of radiation exposure might influence the effectiveness of total-body radiation exposure. Report No. 29 had attempted to provide a means of predicting recovery from radiation injury by introducing the concept of Equivalent Residual Dose (ERD). The ERD formula, based largely on results of experiments on mice, was modified empirically to predict human recovery rates. The ERD formula is considered to be an adequate basis for making large scale pre-attack radiation casualty predictions, but leaves unfulfilled the need for some guidance scheme on which those in charge could base their decisions concerning exposed individuals or groups of persons under operational conditions dur-

ing and after a nuclear attack. The NCRP has attempted to provide this more practical base in this revision of Report No. 29.

This report was prepared to assist in preparedness activities for large disasters in which exposure of many people to nuclear radiation is of primary concern. In particular, those officially responsible for civilian preparedness against nuclear attack should find this report a basic resource for their task. It is an attempt to describe the important characteristics of radiation, with emphasis on radioactive fallout, and radiation injury so that they can be understood by people who will be responsible for decision-making in civil defense operations in a nuclear attack. The recommendations must be regarded as reflecting the NCRP's best effort to evaluate information presently available; they may be modified as more knowledge becomes available.

The present report was prepared by Scientific Committee 14 on Radiological Factors Affecting Decision-Making in a Nuclear Attack. Serving on the Committee during the preparation of this report were: G. V. Leroy, Chairman (1968–1970), G. W. Casarett, Chairman (1970). The members were: E. L. Alpen; J. L. Bateman; H. A. Blair; J. T. Brennan; R. J. Hasterlik; C. C. Lushbaugh; J. H. Rust; and Consultant, J. C. Greene.

The Council wishes to express its appreciation to the members and consultant for the time and effort devoted to the preparation of this report.

Lauriston S. Taylor
President, NCRP

The following are the contents of NCRP Report No. 42: 1. Introduction; 2. General Aspects of Nuclear Weapons; 3. Residual Nuclear Radiation and Fallout; 4. Effects of Radiation on Man; and 5. The Process of Decision-Making.

Appendix A contains the Glossary, and Appendix B, The Use of the "Penalty" Table in Decision-Making (Dose-Time Considerations).

THE AMERICAN RADIUM SOCIETY

FIFTY-SEVENTH ANNUAL MEETING

AMERICANA HOTEL, SAN JUAN, PUERTO RICO
MAY 4–9, 1975

PRELIMINARY PROGRAM

Sunday, May 4, 1975

9:00 A.M.–4:00 P.M. Executive Committee Meeting
9:00 A.M.–5:00 P.M. Registration
6:00 P.M.—Welcoming Reception

Monday, May 5, 1975

9:00 A.M.–9:30 A.M. Opening ceremonies. President's Address. The Role of the Clinician in Community Cancer Control Activities. Victor A. Marcial, M.D., San Juan, Puerto Rico.

9:30 A.M.–1:00 P.M. FIRST SCIENTIFIC SESSION. *Presiding;* Felix N. Rutledge, M.D., Houston, Texas.

9:30 A.M.–11:00 A.M. *Symposium:* The Role of Radiation Therapy in the Management of Primary Breast Carcinoma. *Moderator:* Gilbert H. Fletcher, M.D., M. D. Anderson Hospital, Houston, Texas.

1. Pathology of breast carcinoma. Stephen Gallagher, M.D., M. D. Anderson Hospital, Houston, Texas.
2. Conservative surgery in breast carcinoma. Umberto Veronesi, M.D., Istituto Nazionale Tumori, Milan, Italy.
3. Results in the national clinical trials of primary and adjuvant breast carcinoma treatment. Bernard Fisher, M.D., University of Pittsburgh, Pittsburgh, Pennsylvania.
4. Radiotherapy in the management of primary breast carcinoma. Bernard Pierquin, M.D., Centre Hospitalo-Universitaire Henri Mondor, Creteil, France.
5. Dose and volume of cancer in adenocarcinoma of breast. Gilbert H. Fletcher, M.D., M. D. Anderson Hospital, Houston, Texas.

11:00 A.M.–11:15 A.M. Intermission

11:15 A.M.–11:30 A.M. Subtotal mastectomy (lumpectomy) and radiation therapy in the definitive management of localized breast malignancy. Paul E. Wallner, M.D., and Luther W. Brady, M.D., Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania.

11:30 A.M.–11:45 A.M. Electron beam irradiation for carcinoma of the breast after mastectomy. Norah duV. Tapley, M.D., M. D. Anderson Hospital and Tumor Institute, Houston, Texas.

11:45 A.M.–12:00 Noon. Results of ultrafractionation radiation therapy in breast carcinoma. Harold G. Sutton, M.D., William Fischer, M.D., and Melvin L. Griem, M.D., Franklin McLean Memorial Research Institute, Chicago, Illinois.

12:00 Noon–12:15 P.M. Malignant pericardial effusion. Nael Martini, M.D., Alvin H. Freiman, M.D., Robin C. Watson, M.D., and Basil S. Hilaris, M.D., Memorial Sloan-Kettering Cancer Center, New York, New York.

12:15 P.M.–12:30 P.M. The value of high dose radiation therapy in the treatment of glioblastoma multiforme: a preliminary report. Omar M. Salazar, M.D., Philip Rubin, M.D., Daniel Bassano, Ph.D., Lowell Lapham, M.D., Joseph McDonald, M.D., and Colin Poulter, M.B.B.S., University of Rochester Cancer Center, Rochester, New York.

12:30 P.M.–12:45 P.M. Fast neutron beam radiotherapy of glioblastoma multiforme at the University of Washington. Robert G. Parker, M.D., Herbert C. Berry, M.D., Arthur J. Gerdes, M.D., and Michael D. Soronen, M.D., University Hospital, Seattle, Washington.

12:45 P.M.–1:00 P.M. Randomized study of two dose schedules in radiotherapy of glioblastoma multiforme. Fransiska Lee, M.D., Carlos A. Pérez, M.D., and William E. Powers, M.D., Edward Mallinckrodt Institute of Radiology, St. Louis, Missouri.

6:30 P.M. Night in Old San Juan.

Tuesday, May 6, 1975

7:30 A.M. First Executive Session for all Members· Breakfast Meeting.

9:00 A.M.–1:00 P.M. SECOND SCIENTIFIC SESSION. *Presiding:* Alfred S. Ketcham, M.D., Miami, Florida.

9:00 A.M.–10:30 A.M. *Symposium:* Prevention of Metastases. *Moderator:* Vincent DeVita, M.D., National Cancer Institute, Bethesda, Maryland.

1. Concepts for treatment of micrometastases developed in murine systems. Frank Schabel, M.D.
2. Clinical results with combined modalities.
   - A. Surgery and chemotherapy. George Canellos, M.D., Medical Branch, National Cancer Institute, Bethesda, Maryland.
   - B. Surgery and immunotherapy. Fred Eilber, M.D., University of California, Los Angeles, California.
   - C. Radiotherapy and chemotherapy. Ralph Johnson, M.D., National Cancer Institute, Bethesda, Maryland.

10:30 A.M.–10:45 A.M. Effect of therapeutic irradiation in the immune response. James M. Slater, M.D., Ernest Ngo, M.D., and H. S. Lau, Ph.D., Loma Linda University Medical Center, Loma Linda, California.

10:45 A.M.–11:00 A.M. Intermission.

11:00 A.M.–11:15 A.M. The effect of different modalities of cancer treatment on the immunity to an antigenic transplantable fibrosarcoma (METH A). Mehat Khafagy, M.D., Harold Wanebo, M.D., Alan Alfieri, B.S., and Eric W. Hahn, Ph.D., Memorial Sloan-Kettering Cancer Center, New York, New York. (Sponsored by Edward J. Beattie, M.D.)

11:15 A.M.–11:30 A.M. Transformation delay of lymphocytes from patients undergoing radiotherapeutic treatments. Timothy Merz, Ph.D., and Tapan Hazra, M.D., M.R.C.P., F.F.R., The Johns Hopkins Hospital, Baltimore, Maryland.

11:30 A.M.–11:45 A.M. Gallium-67 scans in children with solid tumors. Philip LaPonte, M.D., Jeffrey Rosenstock, M.D., Philip Littman, M.D., Milton Donaldson, M.D., and David Kuhl, M.D., University of Pennsylvania and The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania.

11:45 A.M.–12:00 Noon. Staging laparotomy in Hodgkin's and non-Hodgkin's lymphomas. Umberto Veronesi, M.D., Istituto Nazionale Tumori, Milan, Italy.

12:00 Noon—12:15 P.M. Histologic characteristics correlated with survival patterns in non-Hodgkin's lymphoma. H. Jung Ree, M.D., Herber Fanger, M.D., and Arvin S. Glicksman, M.D., Rhode Island Hospital and Brown University, Providence, Rhode Island.

12:15 P.M.–12:30 P.M. Mediastinal Hodgkin's disease. Jerome M. Vaeth, M.D., West Coast Cancer Foundation, San Francisco, California; and Steven A. Moskowitz, M.D., School of Medicine, University of California, Davis, California.

12:30 P.M.–12:45 P.M. Observations in the total body electron therapy of mycosis fungoides. Anam Sudarsanam, M.D., Komanduri Charyulu, M.D., Pavel Houdek, M.D., and Herbert Rurnier, M.D., University of Miami, Miami, Florida.

12:45 P.M.–1:00 P.M. Cancer of the undescended or maldescended testis. Mostafa A. Batata, M.D., Willet F. Whitmore, Jr., M.D., Basil S. Hilaris, M.D., Harry Bragstald, M.D., and Nobuhiko Tokita, M.D., Memorial Sloan-Kettering Cancer Center, New York, New York.

Wednesday, May 7, 1975

7:30 A.M. Second Executive Session for all Members. Breakfast Meeting.

9:30 A.M.–1:00 P.M. Third Scientific Session. *Presiding:* Luther W. Brady, M.D., Philadelphia, Pennsylvania.

9:00 A.M.–10:30 A.M. *Symposium:* Management of Carcinoma of the Endometrium. *Moderator:* Felix N. Rutledge, M.D., M. D. Anderson Hospital, Houston, Texas.

1. Estrogen receptors and the estrone hypothesis in relation to endometrial and breast cancer. Creighton Edwards, M.D., University of Texas Southwestern Medical School, Dallas, Texas.
2. Chemotherapy of disseminated or recurrent endometrial cancer. Julian P. Smith, M.D., M. D. Anderson Hospital, Houston, Texas.
3. The role of postoperative irradiation in the management of endometrial carcinoma. Paul Morrow, M.D., University of Southern California, Los Angeles, California.
4. Irradiation of endometrial cancer. José Sala, M.D., Cox Medical Center, Springfield, Missouri.

10:30 A.M.–10:45 A.M. Endometrial cancer in patients with medical contraindication to surgery or unresectable lesions. R. C. Landgren, M.D., G. H. Fletcher, M.D., L. Delclos, M.D., and T. Wharton, M.D., M. D. Anderson Hospital, Houston, Texas.

10:45 A.M.–11:00 A.M. Intermission.

11:00 A.M.–11:15 A.M. Preoperative radiation therapy in endometrial carcinoma: preliminary report of a clinical trial. Irving J. Weigensberg, M.D., Methodist Hospital, Peoria, Illinois.

11:15 A.M.–11:30 A.M. Experience with afterloading Heyman capsules in endometrial cancer. Norman Simon, M.D., and Sidney M. Silverstone, M.D., The Mount Sinai School of Medicine, New York, New York.

11:30 A.M.–11:45 A.M. Treatment and result of 115 cases of Stage I and II sarcomas of the corpus uteri. Vitune Vogtama, M.D., John R. Karlen, M.D., Steven M. Piver, M.D., and Yosiaki Tsukada, M.D., Roswell Park Memorial Institute, Buffalo, New York.

11:45 A.M.–12:00 Noon. *Resident Award:* Inherent cellular radiosensitivity of human tumors of varying clinical curability. Ralph R. Weichselbaum, M.D., J. Epstein, M.D., and John B. Little, M.D., Harvard School of Public Health and Joint Center for Radiation Therapy, Boston, Massachusetts.

12:00 Noon–1:00 P.M. THE JANEWAY LECTURE. Ovarian cancer: multifacet disease; multifarious therapy and therapists. George C. Lewis, Jr., M.D., Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania.

2:30 P.M. Tour of Botanical Gardens.

Thursday, May 8, 1975

9:00 A.M.–1:00 P.M. Fourth Scientific Session.

Presiding: Richard Jesse, M.D., Houston, Texas.

9:00 A.M.–10:30 A.M. *Symposium:* The Place of Interstitial Therapy in Today's Radiotherapy. *Moderator:* Fernando G. Bloedorn, M.D., New England Medical Center Hospital, Boston, Massachusetts.

1. Volume and time factors in interstitial gamma ray therapy. Gilbert H. Fletcher, M.D., M. D. Anderson Hospital, Houston, Texas.
2. Low energy gamma radionuclides for permanent interstitial implantation. Basil S. Hilaris, M.D., Memorial Sloan-Kettering Cancer Center, New York, New York.
3. Squamous cell carcinoma of the oral tongue and floor of mouth: evaluation of some radiotherapy aspects. Luis Delclos, M.D., M. D. Anderson Hospital, Houston, Texas.
4. The destiny of curietherapy in oncology, Bernard Pierquin, M.D., Universitaire Henri Mondor, Creteil, France.

10:30 A.M.–10:45 A.M. Treatment of connective tissue sarcoma by combined simultaneous surgery and implantation of radioactive isotopes. Frank Ellis, M.D., Memorial Sloan-Kettering Cancer Center, New York, New York.

10:45 A.M.–11:00 A.M. Intermission

11:00 A.M.–11:15 A.M. Interstitial radiation in the treatment of carcinoma of the faucial arch. David D. Beiler, M.D., Geisinger Medical Center, Danville, Pennsylvania.

11:15 A.M.–11:30 A.M. External and interstitial radiotherapy of carcinoma of oral tongue—a review of 32 years experience. Karen K. Fu, M.D., J. Warner Ray, M.D., Theodore L. Phillips, M.D., and Eric K. Chan, M.D., University of California, San Francisco, California.

11:30 A.M.–11:45 A.M. Non-randomized comparison of radiation therapy alone and preoperative irradiation combined with radical surgery in the treatment of carcinoma of the tonsil. Carlos A. Pérez, M.D., Fransiska Lee, M.D., L. V. Ackerman, M.D., J. H. Ogura, M.D., and William E. Powers, M.D., Mallinckrodt Institute of Radiology, St. Louis, Missouri.

11:45 A.M.–12:00 Noon. Combined therapy in advanced carcinoma of the oral cavity and oropharynx: a randomized study. Theodore Lo, M.D., Albert Wiley, M.D., Ph.D., Frank F. Gollin, M.D., Fred J. Ansfield, M.D., James A. Brandenburg, M.D., and Guillermo Ramírez, M.D., University of Wisconsin Hospitals, Madison, Wisconsin.

12:00 Noon–12:15 P.M. Initial evaluation of reduced fractionation in the irradiation of malignant epithelial tumors. Maurice Greenberg, M.D., Donald R. Eisert, M.D., and James D. Cox, M.D., The Medical College of Wisconsin, Milwaukee, Wisconsin.

12:15 P.M.–12:30 P.M. Experience with twice-daily fractionation in clinical radiotherapy. L. J. Shukovsky, M.D., G. H. Fletcher, M.D., E.D. Montague, M.D., and H. R. Withers, M.D., M. D. Anderson Hospital, Houston, Texas.

12:30 P.M.–12:45 P.M. Present status of the National Cancer Plan. Guy Newell, M.D., National Cancer Institute, Bethesda, Maryland.

12:45 P.M.–1:00 P.M. The extramural programs of the National Cancer Institute. William A. Walter, M.D., National Cancer Institute, Bethesda, Maryland.

7:00 P.M. Reception—Pool Side.

8:00 P.M. Annual Banquet.

Friday, May 9, 1975

9:00 A.M.–1:00 P.M. Fifth Scientific Session. *Presiding:* Jerome M. Vaeth, M.D., San Francisco, California

9:00 A.M.–10:30 A.M. *Symposium:* Multidisciplinary Approach to the Management of T_3 and T_4 Lesions of the Head and Neck. *Moderator:* Oscar M. Guillamondegui, M.D., M. D. Anderson Hospital, Houston, Texas.

1. Treatment of advanced lesions of the pharynx and larynx. Rodney Million, M.D., University of Miami, Gainesville, Florida.
2. Surgical treatment of advanced carcinoma of the floor of the mouth. Oscar M. Guillamondegui, M.D., M. D. Anderson Hospital, Houston, Texas.
3. Immunotherapy in advanced lesions of the head and neck. Frederick Eilber, M.D., University of California, Los Angeles, California.
4. The role of chemotherapy in advanced lesions of the head and neck. Thomas Pomeroy, M.D., Radiation Therapy Services, Radiation Branch, National Cancer Institute, Bethesda, Maryland.
5. Oropharyngeal carcinoma: results of megavoltage radiation therapy. Malcolm A. Bagshaw, M.D., Stanford University Hospital, Stanford, California.

10:30 A.M.–10:45 A.M. Immunological evaluation of patients with lesions of head and neck. Stefano Stefani, M.D., Ronald Kerman, Ph.D., and Joseph Abbate, M.D., V. A. Hospital, Hines, Illinois.

10:45 A.M.–11:00 A.M. Intermission.

11:00 A.M.–11:15 A.M. Installation of Officers.

11:15 A.M.–11:30 A.M. Factors that modify the radioresponse of cancer of the nasopharynx. Joseph Bohorquez, M.D., D.M.R.T., F.F.R., Downstate Medical Center, Brooklyn, New York.

11:30 A.M.–11:45 A.M. The place of radiotherapy in the definitive management of rectal carcinoma. S. Rafla-Demetrious, M.D., Ph.D., and S. Turner, M.D., The Methodist Hospital, Brooklyn, New York.

11:45 A.M.–12:00 Noon. The proper management of superior vena caval obstruction. Charles Scarantino, M.D., Ph.D., Omar M. Salazar, M.D., and Philip Rubin, M.D., University of Rochester Cancer Center, Rochester, New York.

12:00 Noon–12:15 P.M. Comparison of split-course radiotherapy and continuous radiotherapy for unresectable bronchogenic carcinoma: five-year results. Robert E. Lee, M.D., David T. Carr, M.D., and Donald S. Childs, M.D., Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

12:15 P.M.–12:30 P.M. Radiation injuries of the lung: clinical syndrome, high risk factors, and guidelines for safer practice. Bernard Roswit, M.D., and David White, M.D., Veterans Administration Hospital, Bronx, New York.

12:30 P.M.–12:45 P.M. Enhanced radiation response of small pulmonary metastases of the Lewis lung carcinoma. William U. Shipley, M.D., Judith A. Stanley, M.D., and G. Gordon Steel, M.D., Institute of Cancer Research, Royal Marsden Hospital, Sutton, Surrey, England. (Sponsored by Herman D. Suit, M.D.)

12:45 P.M.–1:00 P.M. Initial comparative response of metastatic superficial nodules surrounding and underlying normal tissue to peak pions and x-rays. Morton M. Kligerman, M.D., Charles J. Sternhagen, M.D., Frances Dobrowolski, M.D., H. T. Davis, Ph.D., J. Edward Barnes, Ph.D., Thomas F. Lane, M.D., James N. Bradbury, Ph.D., Edward A. Knapp, Ph.D., Garry W. West, M.D., and Donald S. Petersen, Ph.D., University of New Mexico, Albuquerque, New Mexico and Los Alamos Scientific Laboratory, Los Alamos, New Mexico.

1:00 P.M. Adjournment of the Fifty-seventh Annual Meeting.

NEWS ITEMS

POSTGRADUATE COURSE ON RADIOLOGY OF THE CHEST

The Department of Radiology of the New York Medical College will hold a "Postgraduate Course on Radiology of the Chest," at the Plaza Hotel, Fifth Avenue at 59th Street, New York, New York, April 7–9, 1975.

The Course has approval for Category 1 credit 17 hours of AMA (through the cosponsorship of the ACR).

The faculty consists of Emil J. Balthazar, M.D., New York, New York; Walter Berdon, M.D., New York, New York; Yahya M. Berkmen, M.D., New York, New York; Kent Ellis, M.D., New York, New York; Benjamin Felson, M.D., Cincinnati, Ohio; Robert G. Frazer, M.D., Montreal, Quebec; Richard M. Friedenberg, M.D., New York, New York; Rita F. Girolamo, M.D., New York, New York; Robert Heitzman, M.D., Syracuse, New York; Bedros Markarian, M.D., Syracuse, New York; Harold Moroson, Ph.D., New York, New York; Stanley S. Siegelman, M.D., Baltimore, Maryland; Natalie S. Strutynsky, M.D., New York, New York; and Manuel Viamonte, Jr., M.D., Miami, Florida.

For hotel reservations, please write to: Ms. Anne Troy, The Plaza Hotel, Fifth Avenue at 59th Street, New York, New York 10019.

POSTGRADUATE COURSE IN PULMONARY RADIOLOGY

Indiana University School of Medicine, Indianapolis, Indiana, presents a "Postgraduate Course in Pulmonary Radiology" on April 23–25, 1975.

This course will review basic chest roentgenography as well as present current concepts of respiratory diseases. Roentgenographic manifestations, pathogenesis and diagnostic methods will be emphasized.

All sessions will be held at the Hilton Hotel. A block of rooms is being held an participants will be sent a hotel reservatio card upon registering for the course. "Th hotel has requested that participants us the registration card." If a participant doe make a phone reservation—please mentio attendance at this course. Rooms will b held until April 4, 1975.

This Continuing Medical Education ac tivity is acceptable for 18 credit hours i Category 1 for the Physician's Recognitio Award of the A.M.A. The program is als acceptable for 18 hours credit by th American Academy of Family Physician The ACGPOMS has approved this cours on an hour for hour basis.

In addition to the Indiana Universit School of Medicine Faculty, the Gues Faculty will include: Joseph J. Booksteir M.D., San Diego, California; John A Campbell, M.D., Los Angeles, California S. Donald Greenberg, M.D., Houstor Texas; R. I. Macpherson, M.D., Winnipeg Manitoba, Canada; Walter E. Mille M.D., Rochester, Minnesota; Kenneth M Moser, M.D., San Diego, California; Ed ward C. Rosenow, III, M.D., Rochester Minnestota; William W. Stead, M.D Little Rock, Arkansas; Jack L. Westcott M.D., Hartford, Connecticut; and Jerom F. Wiot, M.D., Cincinnati, Ohio.

For further information, please contact Indiana University School of Medicine Division of Postgraduate and Continuin Medical Education, 1100 West Michiga Street, Indianapolis, Indiana 46202.

SCIATICA AND LOW BACK PAIN

The Long Island Jewish Hillside Medica Center, New Hyde Park, New York, an nounces a one-day Seminar on "Sciatic and low back pain . . . the stenotic lumba canal and the ridge-disk syndrome" to b held at the Jewish Institute for Geriatri Care, New Hyde Park, New York, May 2 1975, 9 A.M. to 5 P.M.

This Seminar will be conducted by Drs. Bernard S. Epstein, Joseph A. Epstein, Andrew A. Fischer, Robert Greenwald, Leroy S. Lavine, Morton Nathanson, Walter H. Rubens, Jan Smulewicz and Philip Sumner.

The Course is open to orthopedic surgeons, neurologic surgeons, neurologists, radiologists, family physicians, rheumatologists, and is acceptable for 7 Credit hours in Category 1 for the Physicians Recognition Award of the AMA.

For further information, please write to: Office of the Dean of the Clinical Campus, Long Island Jewish-Hillside Medical Center, New Hyde Park, New York 11040.

COURSE IN NEURORADIOLOGY

Columbia-Presbyterian Medical Center

The Department of Radiology, College of Surgeons, Columbia University, announces a postgraduate "Course in Neuroradiology" to be held at the Columbia-Presbyterian Medical Center, under the direction of Ernest H. Wood, M.D., and Sadek K. Hilal, M.D., Ph.D., May 5–9, 1975.

The course is a comprehensive review of diagnostic neuroradiology and is designed primarily for radiologists, neurologists, and neurologic surgeons.

Emphasis will be placed on basic information used frequently in neuroradiologic diagnosis, especially angiography. Computerized tomography will be dealt with in 17 of the 50 lectures and discussions of the course. Other topics include plain film diagnosis, pneumography, myelography, radiology of the orbits and temporal bones, and neuroradiologic approaches to the solution of specific clinical problems.

Inquiries should be addressed to: Jose M. Ferrer, Jr., M.D., Associate Dean of College of Physicians & Surgeons, 630 West 168th Street, New York, New York 10032.

HEAD AND NECK CANCER SYMPOSIUM

This 2 day multidisciplinary approach has been arranged by the Departments of Radiation Therapy, Otorhinolaryngology, and Surgery, Indiana University School of Medicine, Indianapolis, Indiana, May 8–9, 1975.

An outstanding Guest Faculty will join with members of the Indiana faculty as speakers.

For more information, please contact: Division of Postgraduate Medical Education, Indiana University School of Medicine, 1100 West Michigan Street, Indianapolis, Indiana 46202.

INSERM (NATIONAL INSTITUTE OF HEALTH AND MEDICAL RESEARCH) SYMPOSIUM

Recent Progress in Cerebral Angiography

The Institut National de la Santé et de la Recherche Médicale (INSERM) sponsors a Symposium on "Recent Progress in Cerebral Angiography" to be held at Marseille France, May 13–16, 1975.

The topics considered are: anatomy; equipment and techniques; the physiology and biochemistry related to cerebral angiography; and diagnostic advances in angiography.

For further information and registration, please write to: Pr. G. Salamon—Hôpital de la Timone—13005 Marseille, France.

INTERNATIONAL SYMPOSIUM ON "THE CLINICAL USEFULNESS OF HIGH ENERGY RADIATION IN CANCER MANAGEMENT"

The Radiation Therapy Center of Thomas Jefferson University Hospital is sponsoring an International Symposium on "The Clinical Usefulness of High Energy Radiation (6–45 MeV photons and electrons) in Cancer Management" on May 22–24, 1975.

The Symposium will bring together internationally recognized radiation oncologists, medical physicists and radiation biologists to discuss in depth current practice, dosimetry techniques, and clinical results and draw attention to new horizons.

The Guest Faculty will include: Peter Almond, Ph.D., M. D. Anderson Hospital and Tumor Institute, Houston, Texas; Fernando G. Bloedorn, M.D., New En-

gland Medical Center Hospital, Boston, Massachusetts; Andree Dutreix, Ph.D., Institut Gustave Roussy, Paris, France; Jean Dutreix, M.D., Institut Gustave Roussy, Paris, France; Dieter Fehrentz, Ph.D., Universitäts Strahlenklinik, Heidelberg, Germany; Gilbert Fletcher, M.D., M. D. Anderson Hospital and Tumor Institute, Houston, Texas; Jack Fowler, Ph.D., Gray Laboratories, Middlesex, England; Eric Hall, Ph.D., Columbia-Presbyterian Medical Center, New York, New York; John H. C. Ho, M.D., Institute of Radiology, Kowloon, Hong Kong; Harold Johns, Ph.D., Ontario Cancer Institute, Toronto, Ontario, Canada; John Laughlin, Ph.D., Memorial Sloan-Kettering Cancer Center, New York, New York; Carlos Perez, M.D., Washington University School of Medicine, St. Louis, Missouri; W. Pohlit, Ph.D., Max Planck Institute of Biophysik, Frankfurt, Germany; William Powers, M.D., Washington University School of Medicine, St. Louis, Missouri; W. Schumacher, M.D., Rudolf Virchow Krankenhaus, Berlin, Germany; Herman Suit, M.D., Ph.D., Massachusetts General Hospital, Boston, Massachusetts; Norah DuV. Tapley, M.D., M. D. Anderson Hospital and Tumor Institute, Houston, Texas; and Thomas A. Watson, M.B., Ontario Cancer Foundation, London, Ontario, Canada.

The Symposium will be held in the Solis-Cohen Auditorium, Jefferson Alumni Hall, Philadelphia, Pennsylvania.

For advance registration and further particulars, please write to: Dr. Simon Kramer, Chairman, Department of Radiation Therapy, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania 19107.

FIFTH ANNUAL THERAPIST CLINICAL RESEARCH SEMINAR

A Seminar titled "5th Annual Radiotherapist Clinical Research Seminar" will be held at the Flagler Inn in Gainesville, Florida, May 15–17, 1975.

The Seminar will update radiotherapists in new cancer treatment techniques and management. Topics to be covered will be head and neck cancer, lymphomas, gynecologic cancer and miscellaneous presentations.

For further information, please contact: Rodney Million, M.D., Program Director, University of Florida, J. Hillis Miller Health Center, Gainesville, Florida 32601.

CURRENT CONCEPTS IN RADIATION THERAPY

The Department of Therapeutic Radiology and the Office of Continuing Medical Education and Extension, University of Minnesota, announce a Postgraduate Course on the "Current Concepts in Radiation Therapy," to be held at the Mayo Memorial Auditorium, Minneapolis, Minnesota, May 28–30, 1975.

This Course is designed primarily for therapeutic radiologists, general radiologists, and residents. The Course will present comprehensive reviews on tumors of the central nervous system, breast cancer, Hodgkin's disease and the non-Hodgkin's lymphomas. Areas to be covered will include pathology, treatment techniques, treatment philosophy and complications.

The University of Minnesota adheres to the principle that all persons shall have equal opportunity and access to facilities in any phase of University activity without regard to race, creed, color, sex, age or national origin. Under this principle, educational, cultural, social, housing, extracurricular, and employment opportunities are available to all on an equal basis.

For further information, please write to: Continuing Medical Education, Nolte Center for Continuing Education, University of Minnesota, Minneapolis, Minnesota 55455.

CURRENT CONCEPTS IN RADIOLOGY

Including Diagnosis, Therapy and Nuclear Medicine

The Faculty of the Department of Radiology, Duke University Medical Center will give a 6 day postgraduate course at the Atlantis Lodge, Atlantic Beach, North

Carolina (near Morehead City), July 21–26, 1975.

The scientific program will take place the morning half of each day and will cover current "Concepts in Radiology including Diagnosis, Therapy and Nuclear Medicine." The afternoons and evenings will be free for recreational activities.

The course is designed for radiologists, but open to other physicians whether in training or practice, although enrollment is limited to 75 physicians. A 30 hours of AMA "Category 1" accreditation will be given.

For further information, please contact: Robert McLelland, M.D., Department of Radiology, Box 3808, Duke University Medical Center, Durham, North Carolina 27710.

AMERICAN ASSOCIATION OF PHYSICISTS IN MEDICINE (AAPM)

The topic of the 1975 AAPM Summer School is "The Expanding Role of the Diagnostic Radiological Physicist." This is a 5 day course that will occupy approximately 40 hours of lecture and 6 hours of laboratory time, at Rice University, Houston, Texas, July 27–August 1, 1975.

The content of the course will include a brief review of the basic physics of diagnostic radiology. Additional sessions will emphasize the practical aspects of maintaining radiation control and of insuring consistent, high quality radiologic studies.

Families are encouraged to accompany participants.

Further information is available from: Stewart C. Bushong, Director, 1975 AAPM Summer School, Baylor College of Medicine, Houston, Texas 77025.

PHYSICAL ASPECTS OF NUCLEAR MEDICINE AND QUANTITATIVE RADIOGRAPHY

A Special Summer Program on this subject will be held at M.I.T. from July 28 through August 1, 1975.

This Special Summer Program will deal with the state of the art in physical problems related to nuclear medicine and quantitative radiography.

Special emphasis in nuclear medicine will be placed on instrumentation, radiopharmaceuticals, dosimetry and data processing, as well as specific organ studies and therapy.

The areas of quantitative radiography include transverse section imaging, ionography and computer techniques.

The material should be of value to both physicians and physical scientists working in this area.

The Program is jointly sponsored by the Harvard Medical School and M.I.T. through the Harvard-MIT Program in Health Sciences and Technology. Some tuition grants will be available.

For further information, please write to: Gordon L. Brownell, Ph.D., Director of the Summer Session, Room E19-356, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139.

AMERICAN SOCIETY OF CYTOLOGY

The 23rd Annual Scientific Meeting of the American Society of Cytology will be held at El San Juan Hotel, San Juan, Puerto Rico, November 5–8, 1975.

For further information, please contact: Warren R. Lang, M.D., Secretary-Treasurer, Health Sciences Center, 130 South 9th Street, Suite 1006, Philadelphia, Pennsylvania 19107.

RADIOLOGY OF THE GASTROINTESTINAL SYSTEM

The Sixth in a series of ACR Symposia, approved for credit, Category 1 (15 hours), will be held in Toronto, Canada, November 14–16, 1975.

The faculty for this series of symposia is headed by Bernard S. Wolf, M.D. Joining Dr. Wolf on the Faculty are the following recognized experts on radiology of the gastrointestinal system: Drs. Thomas C. Beneventano, Arthur R. Clemett, Alexander R. Margulis, Richard H. Marshak, Morton A. Meyers, William B. Seaman, and Walter M. Whitehouse.

Registrations will be accepted on a first come—first serve basis.

All registrations and inquiries regarding these Seminars should be sent to: The American College of Radiology, 6900 Wisconsin Avenue, Chevy Chase, Maryland 20015.

SECOND INTERNATIONAL SYMPOSIUM ON THE PLANNING OF RADIOLOGICAL DEPARTMENTS (ISPRAD)

This meeting will be held under the sponsorship of Temple University and the Committee on Department Planning of the ACR in Philadelphia, Pennsylvania, September 26–30, 1976.

The participation of all interested radiologists, architects, and hospital planners is invited. The subjects will include planning of radiologic departments, communications, efficiency and utilization in the radiologic department, development of radiologic planning for newly developing countries, and a section for follow-up on papers and plans presented at the first meeting in Helsinki.

Those interested, please contact: Francis J. Shea, M.D.—Secretary, ISPRAD-II, Symposium Office, Department of Radiology, Temple University, School of Medicine and Hospital, 3401 North Broad Street, Philadelphia, Pennsylvania 19140.

THE FACULTY OF RADIOLOGISTS
Regulations for the Twining Medal

A prize of £50 will be awarded every second year to a Fellow of the Faculty of Radiologists. It will be awarded alternately to a diagnostic radiologist and to a radiotherapist. At the time of submitting the entry, the Fellow must be of less than 6 years' standing. He should present a paper or papers describing the work carried out by him.

Conditions of the Award:

(1) The paper or papers must be the original work of the applicant.

(2) The work must have been done at some time within the 6 years preceding the date of the application.

(3) The material submitted may include published work or an M.D. or Ph.D. thesis. If a joint paper is submitted the applicant must state clearly the part of the work carried out by himself.

In 1975, applications from Fellows who are radiotherapists will be considered, and should be submitted to the Warden of the Fellowship of the Faculty of Radiologists, 28 Portland Place, London, W1N 4DE, by September 26, 1975.

BOOK REVIEWS

Nuclear Hepatology: Clinical and Physiological Aspects of Liver Disease by Radioisotopes. By Masahiro Iio, M.D., Director, Department of Nuclear Medicine and Radiological Sciences, Tokyo Metropolitan Geriatric Medical Center, Tokyo; Instructor, Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Tokyo; Hideo Yamada, M.D., Chief, 1st Division, Department of Nuclear Medicine and Radiological Science, Tokyo Metropolitan Geriatric Medical Center, Tokyo; Kenichi Kitani, M.D., Chief, 1st Division of Clinical Physiology, Department of Physiology, Tokyo Metropolitan Institute of Gerontology, Tokyo; and Yasuhito Sasaki, M.D., Chief, Section of Nuclear Medicine, 2nd Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Tokyo, Japan. Cloth. Pp. 164, with many figures. Price, $23.50. Igaku Shoin Ltd., Tokyo. Exclusive U. S. agents, The Williams & Wilkins Company, 428 East Preston Street, Baltimore, Md. 21202, 1973.

There is a great deal more to nuclear hepatology, or the evaluation of the liver by radiotracers, than the familiar static radiocolloid scan. Many techniques allow investigation of this remarkable organ which presides over the splanchnic circulation and participates in manifold metabolic processes.

Four Japanese authors, each experienced in this field, have produced a text containing useful descriptions of nearly all currently-used tracer methodologies and their applications. These include quantitative measurements of porto-systemic shunting, reticuloendothelial phagocytosis, entero-hepatic circulation of bile salts, storage, transport and excretion of bromosulphothalein and other dyes, radioimmunoassay of alpha-fetoprotein, plasma and urinary clearance of labeled copper and of hepatic and splenic blood flow by inert gas desaturation techniques. Some of these methods (*e.g.*, $C^{14}O_2$ breath analysis) are highly ingenious and merit broader clinical use; others (*e.g.*, intra-arterial injection of labeled particles) fall into the limbo of the capability fallacy: since it can be done it is done despite an unsatisfactory cost-benefit ratio.

The authors summarize their observations in a wide variety of hepatic diseases. Their experience is outstanding in 2 that are little known in this country: idiopathic portal hypertension; and *Schistosomiasis japonica*. They have pioneered in the use of radioiodinated bromosulphothalein to evaluate the constitutional hyperbilirubinemias and as a simple test of abnormal hepatic function. They have followed the work of Bradley and colleagues in measuring biliary transport maximum and storage capacity of this agent.

They employ serial imaging extensively in the differential diagnosis of jaundice, using labeled bromosulphophthalein and rose bengal. In this difficult area of diagnosis, it is possible to disagree with the reliability of criteria such as delayed excretion of tracer and "typical" patterns of incomplete biliary tract obstruction. The role of static imaging to detect hepatic malpositions is well illustrated. The discussion of space-occupying lesions of the liver is relatively brief, but includes mention of the multiple-nuclide approach to differential diagnosis.

The modesty of the authors is evident in the general tone of their text, one that understates their significant contributions in this field. Unfortunately, the text suffers from a serious intrusion of typographical errors and variations in the quality of writing. Certain chapters, such as that dealing with degradation of bile salts in malabsorption, are extremely well written, but others present difficulty for the reader. This reviewer found it necessary to re-read the text in order to concentrate on the valuable contents. The quality of the illustrations is good, although some of the scans selected for reproduction are suboptimal by current standards. There are virtually no scintillation images of the liver. The subject of dynamic radionuclide angiography, a method under investigation in this country to detect "arterialized" hepatic lesions, is omitted.

Despite these reservations, the book should be received with great interest by the nuclear medicine physician, the clinical physiologist and by all other physicians who deal with the diagnosis of hepatic diseases.

Philip M. Johnson, M.D.

Pneumopelvigraphy in Modern Gynecological Diagnostics. By Giorgio Cittadini; in

collaboration with Giorgio Mallarini. Cloth. Pp. 248, with many figures. Price, $25.00. Piccin Medical Books, Via Porciglia 10, 35100 Padova, Italy, 1974.

This monograph reflects the work of the author, who draws upon his extensive clinical experience of more than 1,500 examinations. This work defines the modern day role of this particular examination in a clear and concise manner.

There is a brief introductory chapter which deals with the historic view, including the Italian contributions to this procedure. A chapter, briefly but succinctly, describes the technique, radiation dosage, anatomy, and use of complementary associated procedures which can be done simultaneously, such as histosalpingography and air insufflation of the colon. There is an excellent chapter on the congenital anomalies of the uterus and ovaries.

Illustrations in this book are numerous. Reproductions of roentgenograms are excellent, although slightly separated from the text; but this does not present a problem.

The author candidly admits that the use of the procedure has declined due to the advances of laproscopy. There still is a definite place for the use of this examination in the care of the obstetric-gynecologic patient. The ease and the safety with which the procedure can be done makes it very useful.

Emphasis on a close clinical correlation between gynecologist and radiologist is prudently stressed by the author.

Victor G. Mikity, M.D.

BOOKS RECEIVED

The Systemic Manifestations of Inflammatory Bowel Disease. Edited by William M. Lukash, White House Physician and Chairman, Gastroenterology Clinic and Research Departments, National Naval Medical Center, Bethesda, Md.; and Raymond B. Johnson, Assistant Chairman, Gastroenterology Clinic and Research Department, National Naval Medical Center, Bethesda, Md. Cloth. Pp. 356, with some illustrations. Price, $15.50. Charles C Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Ill. 62717, 1974.

Traité de Radiodiagnostic. Tome XVII: Temporal Fosses Nasales Cavités Accessoires. By J. Vignaud, G. L. Dulac, J. François, Y. Guerrier, P. Rabischong, Ph. Tennenbaum, and G. Valvassori. Cloth. Pp. 454, with many figures. Price, 540 F. Masson & Cie, 120 Boulevard Saint-Germain, Paris, France, 1974.

The Biological and Clinical Basis of Radiosensitivity. Edited by Milton Friedman, M.D., Consultant in Radiation Research, Istituto Regina Elena, Rome Italy: Formerly, Professor of Clinical Radiology (Radiation Therapy), New York University School of Medicine; Attending Radiologist (Radiation Therapy), University Hospital; Attending Radiation Therapist, Hospital for Joint Diseases; Visiting Radiation Therapist, Bellevue Hospital; Senior Consultant in Radiation Therapy, Veterans Administration; Consultant in Radiation, Walter Reed General Hospital; Consultant to United States Atomic Energy Commission and United States Public Health Service. Cloth. Pp. 665, with some figures. Price, $49.50. Charles C Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Ill. 62717, 1974.

Röntgenuntersuchung in der Orthopädie: Methode und Technik. By E. Hafner, and H. Ch. Meuli. With a foreword by Professor Dr. med. W. A. Fuchs and Professor Dr. med. M. E. Müller. Cloth. Pp. 199, with 358 figures. Price, geb. Fr. 148.-/DM 141.-. Verlag Hans Huber, Marktgasse 9 und Langgassstrasse 76, Postfach CH 3000 Bern 9, Switzerland, 1975.

Positioning in Radiography. K. C. Clark, M.B.E., F.S.R. Volume 2: Specialized Radiography. Ninth edition. Revised by James McInnes, F.S.R., T.E., F.R.P.S. Cloth, Pp. 335, with many illustrations. Price, $32.50. Ilford Limited, William Heinemann Medical Books Ltd. Distributed by Year Book Medical Publishers, Inc., 35 East Wacker Drive, Chicago, Ill. 60601, 1974.

Annual Report, 1973. The Ontario Cancer Institute incorporating The Princess Margaret Hospital. Paper. The Ontario Cancer Institute, 500 Sherbourne Street, Toronto, Ont., Canada, 1974.

Liquid Scintillation Counting. By K. D. Neame, Department of Physiology, University of Liverpool; and C. A. Homewood, Department of Parasitology, School of Tropical Medicine, University of Liverpool. Cloth. Pp. 180, with some figures. Price, $13.75. Halsted Press. A Division of John Wiley & Sons, Inc., 605 Third Avenue, New York, N.Y. 10016, 1974.

Media 70's National Conference on Multimedia in the Health Sciences Proceedings: Sheraton Gibson Hotel, Cincinnati, Ohio, July 18–21, 1971. Paper. Pp. 290, with some figures. Educational Communications Foundation, Inc., 3150 Spring Street, Fairfax, Va. 22030, 1971.

SOCIETY PROCEEDINGS

MEETINGS OF RADIOLOGICAL SOCIETIES*

United States of America

American Roentgen Ray Society
Secretary, Dr. James Franklin Martin, 300 S. Hawthorne Rd., Winston-Salem, N. C. 27103. Annual Meeting: Marriott Hotel, Atlanta, Ga., Sept. 30–Oct. 3, 1975.

American Radium Society
Secretary, Richard H. Jesse, Dept. of Surgery, M. D. Anderson Hosp. and Tumor Institute, Houston, Tex. 77025. Annual Meeting: Americana Hotel, San Juan, Puerto Rico, May 4–9, 1975.

Radiological Society of North America
Secretary, Dr. Theodore A. Tristan, Harrisburg, Pennsylvania. Annual Meeting: McCormick Place on the Lake, Chicago, Ill., Nov. 30–Dec. 5, 1975.

American College of Radiology
Executive Director, William C. Stronach, 20 N. Wacker Drive, Chicago, Ill. 60606. Annual meeting: Portland-Hilton Hotel, Portland, Oregon, March 31–April 4, 1975.

Section on Radiology, American Medical Association
Secretary, Dr. Antolin Raventos, Davis, Calif. Annual Meeting: Atlantic City, N. J., June 15–19, 1975.

American Board of Radiology
Secretary, Dr. C. Allen Good. Correspondence should be directed to Kahler East, Rochester, Minn. 55901.

Written Examination will be held in 14 selected sites, June 21, 1975.

Oral examinations will be held: Pittsburgh Hilton, Pittsburgh, Pa., June 2–7, 1975; Statler Hilton, Dallas, Texas, Dec. 8–13, 1975; Marriott Motor Hotel, Chicago, Ill., June 14–19, 1976; Sheraton Biltmore, Atlanta, Ga., Dec. 6–11, 1976.

Applications must be received in the Board Office before Sept. 30 of the year preceding the one in which the candidate wishes to be examined.

Deadline for filing applications for any examination in 1976 is September 30, 1975.

American Board of Nuclear Medicine, Inc. A Conjoint Board of the American Boards of Internal Medicine, Pathology and Radiology and sponsored by the Society of Nuclear Medicine.

Application forms and further information are available from the American Board of Nuclear Medicine, 305 E. 45th St., New York, N. Y. 10017.

American Association of Physicists in Medicine
Secretary, Kenneth D. Williams, M.S., Dept. Radiol., Washington Hospital Center, 110 Irving St., N.W., Washington, D. C. 20010. Annual Meeting.

American Society of Therapeutic Radiologists
Secretary, Dr. Robert W. Edland, 1836 South Ave., La Crosse, Wis., 54601. Annual Meeting: Hyatt Regency Hotel in the Embarcadero Center, San Francisco, Calif., Oct. 8–12, 1975.

American Nuclear Society
Program Chairman, Werner K. Kern, IRD, Space Nuclear Systems, F 309, U. S. Atomic Energy Commission, Washington, D.C. 20545.

American Institute of Ultrasound in Medicine
Secretary, John M. Reid, Ph.D., 556 18th Ave., Seattle, Wash. 98122. Annual Meeting.

American Society of Neuroradiology
Secretary, Dr. David O. Davis, Department of Radiology, 901 Twenty-third St., N.W., Washington, D. C. 20037. Annual Meeting.

Fourteenth International Congress of Radiology
Rio de Janeiro, Brazil, Oct. 23–29, 1977.

International Society of Radiology
Hon. Secretary-Treasurer, Prof. W. A. Fuchs, M.D., Department of Diagnostic Radiology, University Hospital, Inselspital, CH-3010 Bern, Switzerland.

Eleventh Inter-American Congress of Radiology
Counselor for the United States, Dr. Juan A. del Regato, Univ. of South Florida, College of Medicine, Tampa, Fla.
Secretary of Congress, Dr. Alberto Mejia, Apartado Aéreo 53737, Bogotá 2, Colombia. Meeting: Feb. 16–21, 1975.

Inter-American College of Radiology
President, Dr. Miguel Dao y Dao, Apartado Postal 14213, Candelaria, Caracas, Venezuela, S.A.
Secretary of Congress: Dr. Alberto Mejia, Apartado Aéreo 53737, Bogotá 2, Colombia, S.A. Meeting: Bogotá, Colombia, Feb. 16–21, 1975.

Third Congress of the European Association of Radiology
Secretary-General, P.O. Box 14, 79 Lauriston Place, Edinburgh BHI IDB, Scotland, Meeting: June 22–27, 1975

Second Asian and Oceanian Congress of Radiology
Secretary, Dr. Buenaventura U. V. Angtuaco, Congress Secretariat Headquarters, 2161 Taft Ave., Manila, Philippines. Meeting: Manila, Philippines, Nov. 10–14, 1975.

Alabama Chapter of ACR
Secretary-Treasurer, Dr. Lawrence E. Fetterman, 1720 Springhill Ave., Suite 201, Mobile, Ala. 36604. Meets time and place of Alabama State Medical Association.

Alaska Radiological Society, Chapter ACR
Secretary-Treasurer, Dr. Maurice J. Coyle, 3200 Providence Ave., Anchorage, Alaska 99504.

American Osteopathic College of Radiology
Annual Scientific Meeting: Americana Hotel, Bar Harbor, Fla. Program Administrator: Lawrence J. Jordan, D.O., Suite 21, Ponce American Bldg., 4601 Ponce de Leon Blvd., Coral Gables, Fla. 33146.

American Thermographic Society
Secretary-Treasurer, John Wallace, Ph.D., Dept. Radiol., Thomas Jefferson Univ. Hosp., Philadelphia, Pa. 19107. Annual Meeting.

Arizona Radiological Society, Chapter of ACR
Secretary, Dr. Robert J. Johnson, 1603 N. Tucson Blvd., Tucson 85716. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meeting six months later.

Ark-La-Tex Radiological Society
Secretary, Dr. Erich K. Lang, Confederate Memorial Medical Center, LSU School of Medicine, Shreveport, La. 71101.

Arkansas Chapter of ACR
Secretary-Treasurer, Dr. David H. Newbern, 4301 W. Markham, Little Rock, Ark. 72205. Meets twice annually, the Spring Meeting being in conjunction with and at the place of the State Medical Association.

Association of University Radiologists
Secretary-Treasurer, Dr. Mark M. Mishkin. The Graduate Hosp., Univ. of Pennsylvania, Philadelphia, Pa. 23rd Annual Meeting: San Diego, Calif., May 4–6, 1975.

Atlanta Radiological Society
Secretary-Treasurer, Dr. Marshall J. Cantanzaro, Dept. of Radiol., Northside Hosp., Atlanta, Ga. 30342. Meets on fourth Thursday evenings during the academic year at a

*** Secretaries of societies are requested to send timely information promptly to the Editor.**

time announced in early September of each year, at the Academy of Medicine, Atlanta, Ga., at 8:00 P.M.

BAVARIAN-AMERICAN RADIOLOGIC SOCIETY
Secretary, Maj. Marco J. DiBiase, M.D., Radiology Service, 130 Station Hosp., APO N. Y. 09102. Next Meeting: Berlin, March 14–16, 1975.

BLOCKLEY RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Joseph H. Rosen, West Park Hospital, 3905 Ford Rd., Philadelphia, Pa. 19131.

BLUEGRASS RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Eugene Slusher, Lexington Clinic, 1221 S. Broadway, Lexington, Ky. 40504. The Society meets once each month during the school year.

BRONX RADIOLOGICAL SOCIETY, NEW YORK STATE, CHAPTER ACR
Secretary-Treasurer, Dr. Leon J. Corbin, 1369 Rosendale Ave., Bronx, N. Y. 10472. Meets 4 times a year.

BROOKLYN RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Joshua A. Becker, Downstate Medical Clin., 450 Clarkson Ave., Brooklyn, N. Y. 11203. Meets first Thursday of each month, October through June.

BUFFALO RADIOLOGICAL SOCIETY
Secretary, Dr. George J. Alker, Jr., E. J. Meyer Mem. Hosp., Buffalo, N. Y. 14215. Meets second Monday evening each month, October to May inclusive, at University Club.

CALIFORNIA RADIATION THERAPY ASSOCIATION
Secretary-Treasurer, Dr. James R. Eltringham, Stanford Medical Center, Stanford, Calif. 94304. Meets semiannually in San Francisco and Los Angeles.

CALIFORNIA RADIOLOGICAL SOCIETY, CALIFORNIA CHAPTER OF ACR
Secretary-Treasurer, Dr. John L. Gwinn, 4650 Sunset Blvd., Los Angeles, Calif. 90027.

CATAWBA VALLEY RADIOLOGICAL SOCIETY
Secretary, Dr. Walter Joe Jacumin, P.O. Box 265, Rutherford College, N. C. 28671. Meets the last Thursday of every month, Holiday Inn, Morganton, N. C. at 7:30 P.M.

CENTRAL NEW YORK RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Alfred Brettner, Auburn Mem. Hosp., Auburn, N. Y. 13021. Meets first Monday each month October through May.

CENTRAL OHIO RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Daniel E. Lewis, Grant Hosp., Columbus, Ohio 43215. Meets second Thursday in October, November, January, and March 15, and May 19 at Fort Hayes Hotel, Columbus, Ohio.

CENTRAL TEXAS RADIOLOGY SOCIETY
Secretary-Treasurer, Dr. John M. Stoebner, Scott and White Clinic, Temple, Tex. 76501. Meets the fourth Monday of each month at Ponderosa Hotel, Temple, Tex. at 7:00 P.M.

CHICAGO RADIOLOGICAL SOCIETY, DIVISION OF THE ILLINOIS RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary-Treasurer, Dr. Harold J. Lasky, 55 E. Washington St., Suite 1735, Chicago, Ill. 60602. Meets third Thursday of each month, October to April, except December, at the Bismark Hotel, Chicago, Ill.

CLEVELAND RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Charles M. Greenwald, 7007 Powers Blvd., X-Ray Dept., Parma, Ohio 44129. Meetings at 7:00 P.M. on fourth Monday of October, November, January, February, March and fifth Monday of April.

COLORADO RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary, Dr. Jerome D. Sutherland, 3705 E. Colfax Ave., Denver, Colo. 80206. Meets third Friday of each month at Denver Athletic Club from September through May.

CONNECTICUT VALLEY RADIOLOGIC SOCIETY
Secretary, Dr. Gerald N. LaPierre, 759 Chestnut St., Springfield, Mass. 01107. Meets in April and October.

DALLAS-FORT WORTH RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Richard C. Gasser, 1550 W. Rosedale, Rm. 100, Ft. Worth, Tex. 76104. Meets the 3rd Monday of every month at 6:30 P.M., at the Cibola Inn, Arlington, Tex.

DELAWARE CHAPTER OF ACR
Secretary, Dr. Seymour R. Kaplan, Kent Gen. Hosp., Dover, Del. 19901.

EAST BAY RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Robert L. Stein, 43 Dormidera Ave., Piedmont, Calif. 94611. Meets first Thursday each month, Oct. through May, at University Club, Oakland, Calif.

EAST TENNESSEE RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. George H. Wood, 205 Medical Arts Bldg., Knoxville, Tenn. 37902. Meets in January and September.

FLORIDA RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary, Dr. Paul J. Popovich, 1350 S. Hickory St., Melbourne, Fla. 32901. Meets twice annually, in the spring with the Annual State Society Meeting and in the fall.

FLORIDA WEST COAST RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. James P. Ahearn, 501 E. Buffalo Ave., Tampa, Fla. 33603. Meets on 4th Thursday of the months January, March, May, October, and November.

GEORGIA RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary, Dr. E. P. Rasmussen, Piedmont Prof. Bldg., 35 Collier Rd., N.W., Atlanta, Ga. 30309.

GREATER CINCINNATI RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Owen L. Brown, 2421 Auburn Ave., Cincinnati, Ohio 45219.

GREATER KANSAS CITY RADIOLOGICAL SOCIETY
President-Secretary, Dr. Keith W. Gallehugh, Bethany Med. Center, Kansas City, Kans. Meets 5 times a year.

GREATER LOUISVILLE RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. L. D. LeNeave, 315 E. Broadway, Louisville, Ky. 40202. Meets monthly.

GREATER MIAMI RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Robert F. Conti, Holy Cross Hosp., Fort Lauderdale, Fla. 33308. Meets monthly, third Wednesday at 8:00 P.M. at various member hospitals, Miami, Fla.

GREATER ST. LOUIS SOCIETY OF RADIOLOGISTS
Secretary-Treasurer, Dr. Donald Callahan, Northland Med. Bldg., Jennings, Mo. 63136.

HAWAII RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary-Treasurer, Dr. Sidney B. W. Wong, Straub Clinic and Hosp., Honolulu, Hawaii 96813. Meets third Monday of each month at 7:30 P.M.

HEALTH PHYSICS SOCIETY
Secretary, Russell F. Cowing, P.O. Box 156, E. Weymouth, Mass. 02189. Annual Meeting.

HOUSTON RADIOLOGICAL SOCIETY
Secretary, Dr. Neill B. Longley, 6436 Fannin, Suite 601, Houston, Tex. 77025. Meets fourth Monday of each month, except June, July, August and December, at 6:00 P.M., at 103 Jesse H. Jones Library Building, Texas Medical Center, Houston, Tex. 77025.

IDAHO STATE RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary-Treasurer, Dr. John H. Truksa, 1605 Park Ave., Nampa, Id. 83651. Meets in the spring and fall.

ILLINOIS RADIOLOGICAL SOCIETY, INC., CHAPTER OF ACR
Secretary, Dr. Robert D. Dooley, Hinsdale Med. Center, Hinsdale, Ill. 60521. Meets in the spring and fall.

INDIANA ROENTGEN SOCIETY, INC., CHAPTER OF ACR
Secretary, Dr. John A. Knote, 716 Carrolton Blvd., West Lafayette, Ind. 47906.

IOWA RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary-Treasurer, Dr. John Huston, Jr., 1948 First Ave., N.E., Cedar Rapids, Iowa 52402. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific session is held in the autumn.

KANSAS RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary-Treasurer, Dr. Ralph H. Baehr, 310 Medical Arts Bldg., Topeka, Kan. 66604. Meets in spring with State Medical Society and in winter on call.

Society of Gastro-intestinal Radiologists
Secretary-Treasurer, Dr. John R. Amberg, University Hospital, 225 W. Dickinson St., San Diego, Calif. 92103.

Society of Nuclear Medicine
Secretary, Dr. E. James Potchen, Edward Mallinckrodt Institute of Radiology, 660 S. Euclid Ave., St. Louis, Mo. 63110. *Administrative Officer*, Mrs. Margaret Glos, 211 E. 43rd St., New York, N. Y. 10017. Annual Meeting.

South Bay Radiological Society
Secretary, Dr. Robert Mindalzun, Valley Radiologists, Inc., 100 O'Connor Dr., San Jose, Calif. 95128. Meets the 2nd Monday of each month at the Santa Clara County Medical Society Bldg., 700 Empey Way, San Jose, Calif.

South Carolina Radiological Society, Chapter of ACR
Secretary, Dr. George W. Brunson, 1406 Gregg St., Columbia, S. C. Annual meeting (primarily business) in conjunction with the South Carolina Medical Association meeting in May. Annual fall scientific meeting at time and place designated by the president.

South Coast Radiological Society Chapter of ACR
Secretary-Treasurer, Dr. Richard T. Love, Santa Barbara Med. Clin., 215 Pesetas Lane, Santa Barbara, Calif. 93110. Meets fourth Tuesday of alternate months, Sept., Nov., Jan., March and May.

South Dakota Radiological Society, Chapter of ACR
Secretary, Dr. M. F. Petereit, 2416 S. Phillips, Sioux Falls, S. D. 57105. Meets in spring with State Medical Society and in fall.

Southern California Radiation Therapy Society
Secretary-Treasurer, Dr. Duane J. Gillum, 250 W. Pueblo St., Santa Barbara, Calif. 93105. Meets quarterly.

Southern Radiological Conference
Secretary-Treasurer, Dr. J. W. Maxwell, P.O. Box 2144 Mobile Ala. 36601. Annual Meeting: Grand Hotel, Point Clear, Ala., Jan. 31–Feb. 2, 1976.

Tennessee Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Charles W. Kimsey, 111 Whitehall Bldg., 960 E. Third St., Chattanooga, Tenn. 37403. Meets annually at the time and place of the Tennessee State Medical Association meeting.

Texas State Radiological Society, Chapter of ACR
Secretary, Dr. Francis E. O'Neill, 1128 Nix Prof. Bdg., San Antonio, Tex. 78205.

The Fleischner Society
Secretary, Dr. E. Robert Heitzman, State University of New York Upstate Medical Center, Syracuse, N. Y. 13210. Annual Meeting: St. Francis Hotel, San Francisco, Calif., May 28–31, 1975.

Tri-State Radiological Society
Secretary, Dr. Alfred Lessure, Welborne Hosp., Evansville, Ind. 47714. Meets bimonthly on the third Wednesday at Arco Hospitals.

Upper Peninsula Radiological Society
Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

Utah State Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Patrick D. Lester, Dept. Radiol., University of Utah Medical Center, Salt Lake City, Utah 84112. Meets quarterly at Holy Cross Hospital.

Vermont Radiological Society, Chapter of ACR
Secretary, Dr. J. Lorimer Holm, R.R. #3, Barre, Vt. 05641.

Virginia Chapter of ACR
Secretary-Treasurer, Dr. Charles P. Winkler, 3500 Kensington Ave., Suite 2-A, Richmond, Va. 23221.

Washington, D. C., Chapter of ACR
Secretary-Treasurer, Dr. Robert M. Allen, 9312 Convento Terr., Fairfax, Va. 22030.

Washington State Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Donald J. Hesch, 3216 N.E. 45th Place, Seattle, Wash. 98105.

West Virginia Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Andrew W. Goodwin, II, 200 Med. Arts Bldg., Charleston, W. Va. 25301. Meets concurrently with annual meeting of West Virginia State Medical Society, other meetings arranged by program committee.

Westchester County Radiological Society
Secretary, Dr. James O. Richardson, Jr., 280 Mamaronek Ave., White Plains, N. Y. 10605. Meets on second Tuesday of October, December, February and May.

Wisconsin Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. June Unger, Wood VA Hosp., Wood, Wis. 53193. Meets twice a year, May and September.

Wisconsin Society of Therapeutic Radiologists
Secretary, Dr. Alvin Greenberg, Radiother. Ctr., Univ. Hospitals, Madison, Wis. 53706. Meets quarterly.

Wyoming Radiological Society, Chapter of ACR
Secretary, Dr. Ross J. Collie, Box 96, Lander, Wyo. 82520. Meets in fall with State Medical Society and in spring on call of President.

Mexico, Puerto Rico and Central America

Asociación Costarricense de Radiología
Secretary, Dr. Rafael Umaña-Umaña, Apartado 8-5340, San José, Costa Rica.

Asociacón de Radiólogos de Centro America y Panamá. Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá
Secretary-General, Dr. Francisco Miranbell Solis, Apartado 3352, San José, Costa Rica, Central America. Meets annually in a rotating manner in the six countries.

Asociación Puertorriqueña de Radiología
Secretary, Dr. R. B. Díaz Bonnet, Suite 504, Professional Bldg., Santurce, Puerto Rico.

Sociedad de Radiología de Salvador
Secretary, Dr. Carlos Meijia, 5a Av. Nte. No. 434, San Salvador, Rep. El Salvador.

Sociedad de Radiología de Guatemala
Secretary, Dr. Carlos E. Escobar, 9², Calle A 0–05, Zona 1, Guatemala

Sociedad Mexicana de Radiología, A.C.
Coahuila No. 35, México 7, D.F., México.
Secretary-General, Dr. Jorge Cano Coquí. Meets first Monday of each month.

Sociedad Radiológica Panameña
Secretary, Dr. L. Arrieta Sánchez, Apartado No. 6323, Panamá, R. de P. Meets monthly in a department of radiology of a local hospital chosen at preceding meeting.

Sociedad Radiológica de Puerto Rico
Secretary, Dr. Heriberto Pagán Sáez, Box 9387, Santurce, Puerto Rico. Meets second Thursday of each month at 8:00 P.M. at the Puerto Rico Medical Association Bldg. in San Juan.

British Commonwealth of Nations

Association of Radiologists of the Province of Quebec
121 Boul. Taschereau, Greenfield Park, P. Q., Canada. Meets four times a year.

British Institute of Radiology
Honorary Secretaries, D. H. Traspnell, M. Cohen, 32 Welbeck St., London, W1M/7PG, England.

Canadian Association of Physicists, Division of Medical and Biological Physics
Honorary Secretary-Treasurer, Dr. R. G. Baker, Ontario Cancer Foundation, Ottawa Civic Clinic, 1053 Carling Ave., Ottawa 3, Ont., Canada.

Canadian Association of Radiologists
Honorary Secretary, Dr. Ross O. Hill, Suite 806, 1440 St. Catherine St. West, Montreal 107, Que., Canada. Thirty-eighth Annual Meeting: Toronto, Ont., May 11–16, 1975.

Edmonton and District Radiological Society
Secretary, Dr. L. A. Koller, Suite 360, Professional Bldg., 10830 Jasper Ave., Edmonton 15, Alberta, Canada.

Meets third Thursday of each month October to May, except December, at various Edmonton Hospitals.

FACULTY OF RADIOLOGISTS
Honorary Secretary, P. D. Thomson, 28 Portland Pl., London, W1N 4DE.

MONTREAL RADIOLOGICAL STUDY CLUB
Secretary, Dr. W. Paul Butt, Montreal General Hospital, Montreal, Que., Canada. Meets first Tuesday evening, October to April.

SECTION OF RADIOLOGY OF THE ROYAL SOCIETY OF MEDICINE (CONFINED TO MEDICAL MEMBERS)
Meets third Friday each month at 8:15 P.M. at the Royal Society of Medicine, 1 Wimpole St., London, W. 1 M8AE, 1 England.

SOCIÉTÉ CANADIENNE-FRANÇAISE DE RADIOLOGIE
Secretary-General, Dr. Hubert Sasseville, Verdun Hospital, Montréal, P. Q., Canada. Meets every third Tuesday from October to April.

THE HOSPITAL PHYSICISTS' ASSOCIATION
Honorary Secretary, J. B. Massey, B.Sc., Christie Hosp. and Holt Radium Institute, Physics Department, Withington, Manchester M20 9BX, England.

TORONTO RADIOLOGICAL SOCIETY
Secretary, Dr. George Wortzman, Toronto General Hosp., Toronto 12, Ont., Canada. Meets second Monday of each month, September through May.

THE ROYAL AUSTRALASIAN COLLEGE OF RADIOLOGISTS
Honorary Secretary, Dr. T. P. Loneragan, 45 Macquarie St., Sydney, N.S.W. 2000, Australia.

SOUTH AMERICA

COLÉGIO BRASILEIRO DE RADIOLOGIA
Secretary-General, Dr. Lauro de Abreu Coutinho, Caixa Postal 5984, São Paulo, Brazil.

FEDERACIÓN ARGENTINA DE SOCIEDADES DE RADIOLOGÍA
Branches of the Federation are: Sociedad de Radiólogos de la Provincia de Córdoba; Sociedad Argentina de Radiología; Asociación Argentina de Radiología; Sociedad de Radiología, Radioterapéutica y Medicina Nuclear de Rosario; Sociedad de Radiología y Medicina Nuclear del Centro y Sudeste de la Provincia de Buenos Aires (Mar del Plata); Sociedad Salteña de Radiología y Medicina Nuclear; Sociedad de Radiología de Tucumán; Sociedad de Radiologia del Nordeste Argentino; Sociedad de Radiología de La Plata; and Sociedad de Radiología de San Juan.
Secretary-General-Treasurer, Dr. Roberto Habichayn, Av. Colón 637, Córdoba, Argentina.
Congress will be organized by Sociedad de Radiología, Radioterapéutica y Medicina Nuclear de Rosario in 1975.

SOCIEDAD ARGENTINA DE RADIOLOGÍA
Secretary-General, Dr. Tomás J. Gutiérrez F, Santa Fé 1171, Buenos Aires, Argentina. Meets first Wednesday evening, April through December.

SOCIEDAD BOLIVIANA DE RADIOLOGÍA
Secretary, Dr. Javier Prada Méndez, Casilla 1182, La Paz, Bolivia. Meets monthly. General assembly once every two years.

SOCIEDADE BRASILEIRA DE RADIOLOGIA
Secretary, Dr. Armando Rocha Amoédo, Caixa Postal 1532, Rio de Janeiro, Brazil. General Assembly meets every two years in December.

SOCIEDADE BRASILEIRA DE RADIOTERAPIA
Luiz Antonio, 644, São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

SOCIEDAD CHILENA DE RADIOLOGÍA
Secretary, Dr. Manuel Neira, Casilla 13426, Santiago, Chile. Meets first Friday of each month at Av. Santa María 1810 at 7:00 P.M.

SOCIEDAD COLOMBIANA DE RADIOLOGÍA
Secretary-General, Dr. Gustavo Sánchez Sánchez, Bogotá, Colombia. Meets last Thursday of each month.

SOCIEDAD ECUATORIANA DE RADIOLOGÍA
Secretary, Dr. Luis Blum, Casilla 3712, Guayaquil, Ecuador.

SOCIEDAD PARAGUAYA DE RADIOLOGÍA
Secretary, Dr. Hugo Volpe Rios, 15 de Agosto 322, Asunción, Paraguay.

SOCIEDAD PERUANA DE RADIOLOGÍA
Secretary-General, Dra. Ladis Delpino, Av. General Santa Cruz No. 315, Miraflores, Lima, Perú, Casilla Correo, 2306, Lima, Perú. Meets monthly except during January, February, and March.

SOCIEDAD DE RADIOLOGÍA DEL ATLANTICO
Secretary, Dr. Raul Fernandez, Calle 40 #41-110, Baranquilla, Colombia. Society meets monthly at the Instituto de Radiología.

SOCIEDAD DE RADIOLOGÍA DEL NORDESTE ARGENTINO
Secretary-General, Dr. Francisco J. Velar, Catamarca 561, Corrientes, Argentina.

SOCIEDAD DE RADIOLOGÍA DE LA PLATA
Secretary, Dr. Hiram D. Haurigot, Calle 50 No. 374, La Plata, Argentina.

SOCIEDAD DE RADIOLOGÍA, CANCEROLOGÍA Y FÍSICA MÉDICA DEL URUGUAY
Secretary-General, Dr. Manuel Gonzáles Maseda, Av. Agraciada 1464, piso 13, Montevideo, Uruguay.

SOCIEDADE DE RADIOLOGÍA DE PERNAMBUCO
Secretary, Dr. Manoel Medeiros Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife, Caixa Postal 505, Pernambuco, Brazil.

SOCIEDAD DE ROENTGENOLOGÍA Y MEDICINA NUCLEAR DE LA PROVINCIA DE CÓRDOBA
Secretary-General, Dr. Lucas C. Di Rienzo, Ave. Grl. Paz. 151, Córdoba, Argentina.

SOCIEDAD DE RADIOLOGÍA, RADIOTERAPÉUTICA Y MEDICINA NUCLEAR DE ROSARIO
Secretary-General, Dr. Federico Frágola, Santa Fe 1798, Rosario, Argentina.

SOCIEDAD SALTEÑA DE RADIOLOGÍA Y MEDICINA NUCLEAR
Treasurer, Dr. Julio Luis Baldi, Av. Sarmiento 536, Salta, Argentina.

SOCIEDAD VENEZOLANA DE RADIOLOGÍA Y MEDICINA NUCLEAR
Secretary-General, Dr. Salvador Itriago Borgas, Apartado Postal 9213, Candelaria, Caracas, Venezuela. Meets monthly, third Friday at Colegio Médico del Distrito Federal, Caracas.

CONTINENTAL EUROPE

ÖSTERREICHISCHE RÖNTGEN-GESELLSCHAFT
Secretary, Dr. Ernst Kotcher, Wiener Allgemeine Poliklinik Mariannengasse 10, A-1090 Wien, Austria. Meets second Tuesday of each month in Allgemeine Poliklinik.

SOCIÉTÉ ROYALE BELGE DE RADIOLOGIE
General Secretary, Dr. Joseph Baeyens, Alost, Belgium. Meets in February, March, May, June, September, October, November and December.

SOCIÉTÉ EUROPÉENNE DE RADIOLOGIE PÉDIATRIQUE
Secretary, Dr. J. Corbaton, Clinica Infantil "La Paz," Av. Generalissimo, 117 Madrid 34, Spain. Annual Meeting: Madrid, Apr. 24–26, 1975.
Permanent Secretary, Clément Fauré, Hôpital des Enfants Malades, 149, rue de Sèvres, 75 730, Paris Cadet 15, France.

SOCIÉTÉ FRANÇAISE DE RADIOLOGIE MÉDICALE, MÉDECINE NUCLÉAIRE ET ÉLECTROLOGIE, and its branches: SOCIÉTÉ DU SUD-OUEST, DU LITTORAL MÉDITERRANÉEN, DU CENTRE ET LYONNAIS, DU NORD, DE L'OUEST, DE L'EST, DU MASSIF CENTRAL, D'OUTRE-MER ET D'ÉTRANGER. Parent Society meets third Monday of each month, except during July, August and September, rue de Seine 12, Paris, France.
Secretary-General, Dr. Ch. Proux, 9 rue Daru, Paris 75008, France.

SOCIÉTÉ FRANÇAISE DE NEURORADIOLOGIE
Secretary-General, Professeur agr. R. Djindjian 16, rue de l'Université 75, Paris 7e, France. Annual meeting.

Československá Radiologická Společnost
Secretary, Associate Professor Jaromír Kolář, M.D., Sc.D., Radiological Clinic, Praha 2, U nemocnice 2, Czechoslovakia. Meets monthly except during July, August and September. Annual general meeting.

Deutsche Röntgengesellschaft
President, Professor Dr. med. Walter Frommhold, Director of Medizinisches Strahleninstitut der Universität Tübingen, Röntgenweg 11, 7400 Tübingen, Germany.

Faculty of Radiologists of the Royal College of Surgeons in Ireland
Honor. Secretary, Max. J. Ryan, St. Stephen's Green, Dublin 2. Annual Meeting, Oct. 25 and 26, 1974.

Società Italiana di Radiologia Medica e Medicina Nucleare
Administrative Secretary, Prof. E. Conte, Ospedale Mauriziano, 10128 Torino, Italy. Meets annually.

Societas Radiologica Danica
Secretary, Dr. Bent Langenfeldt, Tretommervej 20a, DK. 8240 Risskov, Denmark.

Nederlandse Vereniging voor Radiologie
Secretary, Dr. J. D. Mulder, Dept. of Rad., Akademisch Ziekenhuis, Leiden, Netherlands.

Scandinavian Radiological Society
Secretary-General, Professor C. F. Unnérus, M.D., Hagalung-Tapiola, Havsvindsvägn 5 C., Finland. Annual Meeting.

Sociedad Española de Radiología y Electrología Médicas y de Medicina Nuclear
Secretary-General, Dr. Pilar Gallar Barberá, Villanueva, 11, Madrid 1, España. Meets every other Saturday evening of each month, Oct. to June, inclusive, in Madrid.

Sociedade Portuguesa de Radiologia e Medicina Nuclear
Secretary-General, Dr. Luís Aires de Sousa, Av. Elias Garcia, 123- 1, Esg.-Lisboa i-Portugal.

Schweizerische Vereinigung für Radiologie, Nuklearmedizin und Strahlenbiologie (Association Suisse de Radiologie, Médecine Nucléaire et de Radiobiologie)
Secretary, Dr. med. Gustav Schoch, Bethesdaspital, Gellerstrasse 144, 4000 Basel, Switzerland.

Asia

Indian Radiological Association
Honor. Gen. Secretary, Dr. S. P. Aggarwal, 10-B Kasturba Ghandi Marg, New Delhi 110001. 28th Indian Congress of Radiology will be held in Hyderabad in 1975.

Indonesian Radiological Society
Secretary, Dr. Gani Iljas Sasmitaatmadja, Radiology Dep., Faculty of Medicine, University of Indonesia, Salemba 6, Jakarta, Indonesia.

Iranian Radiological Society
Secretary, Dr. Majid Rooholamini, P.O. Box No. 14-1151, Teheran, Iran. The Society meets on the second Saturday of each month. 5th Iranian Congress of Radiology, Apr. 12-17, 1975.

Israel Radiological Society
Secretary, Dr. M. A. Lerner, Hesharon Hosp., Petah-Tigva, Israel.

Philippine College of Radiology
Secretary-Treasurer, Dr. Eduardo V. Nievera, Box 1284 Commercial Center, Makati, Rizal D-708, Philippines. Meets every second Thursday of the month.

Radiological Society of Thailand
Secretary, Prof. Rojana Suvansuthi, M.D., Ph.D., Depart. of Rad., Sirizaj Hospital, Faculty of Medicine, Mahidol University, Bangkok 7, Thailand.

Africa

Association of Radiologists of West Africa
Honorary Secretary, C. A. Beetlestone, M.B., B.S., D.M.R.D., Dept. Radiol., University College Hosp., Ibadan, Nigeria.

Radiological Society of South Africa
Secretary, Dr. B. Rosenberg, P.O. Box 3200, Johannesburg, South Africa.

South African International Radiological Congress
Director, Dr. Paul Sneider, P.O. Box 4878, Johannesburg, South Africa.

ABSTRACTS OF RADIOLOGIC LITERATURE

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ROENTGEN DIAGNOSIS

Abdomen

Beckly, D. E. Alimentary tract metastases from malignant melanoma. *Clin. Radiol.*, July, 1974, *25*, 385–389. (From: The United Bristol Hospitals, Bristol, England.)

The alimentary tract is a common site of primary malignant neoplasms and a variety of metastatic tumors. At autopsy, melanotic metastatic lesions are found in the stomach in 26 per cent of the patients and in the small bowel in 58 per cent. The radiographic demonstration of metastatic melanoma within the stomach or small bowel is, however, unusual. The author has reviewed the findings in 3 such cases.

Surgical intervention is to be avoided in metastatic melanotic lesions of the intestine because of the poor prognosis of these patients, but, diagnostic difficulties may arise and surgery become necessary when the intestinal tract is the initial presenting site of a malignant melanoma. In each case there was a prior history of excision of a malignant melanoma, the stool was positive for occult blood, and chest roentgenograms were normal.

In a 31 year old male with malaise, anorexia, and weight loss a large filling defect was found arising from the anterior lateral wall of the stomach at fluoroscopic examination. Laparotomy revealed a second metastatic lesion within the jejunum. In the second case, an 88 year old male presented with vomiting. There were multiple sharply demarcated filling defects in the first part of the duodenum. Lethargy and epigastric discomfort were the symptoms in a 56 year old male who was found at upper gastrointestinal examination to have a deformed duodenal bulb with an ulcerated filling defect in the second part of the duodenum.

The radiographic appearance of metastatic malignant melanoma has previously been described. In the stomach single or multiple large mass lesions often with ulceration may occur. The small bowel is the more common site of involvement with one or more intraluminal filling defects with central ulcerations or umbilications giving rise to the so-called "bull's eye" description. Dilatation and eccentricity of the intestinal lumen and even obstruction, but only in association with intussusception, have also been reported in several cases.

There are myriad differential diagnoses for single or multiple lesions within the stomach or small bowel, and these are detailed by the author.—*John T. Underberg, M.D.*

Cordero, Alejandro A., Gutierrez, Vincente P., and Bugnard, Enrique R. Angiomatosis cutánea gastrointestinal: "blue rubber bleb nevus." (Gastrointestinal cutaneous angiomatosis: "blue rubber bleb nevus.") *Prensa méd. argent.*, 1974, *60*, 54–58. (From: Universidad de Buenos Aires, Facultad de Medicina, Hospital de Clinicas "José de San Martin," Primeras Cátedras de Dermatologia, Cirugía y Pediatría, Buenos Aires, Argentina.)

The authors report a case of multiple visceral-cutaneous hemangiomas. This syndrome is known as "blue rubber bleb nevus syndrome" or the Bean syndrome. This is considered to be a familial-hereditary disorder.

The patient was an 18 year old boy with a history of cutaneous tumors since he was 8 months old. For the last 5 years he had suffered from intermittent intestinal bleeding of severe degree, that had required multiple transfusions. Physical examination disclosed 122 cutaneous hemangiomas scattered throughout the body, and 3 hemangiomas in the mucosae (soft palate and prepucial mucosa). The cutaneous lesions were of a bluish color and of a "rubbery" consistency. Most of them would empty when pressed and would fill rapidly when the local pressure ceased. Gastroscopic examination revealed 4 submucosal hemangiomas in the stomach. The liver was enlarged and a selective hepatic arteriogram revealed a hepatic hemangioma. It was also determined preoperatively that the patient was bleeding from the small bowel.

At surgery, the presence of the gastric and hepatic angiomas was confirmed. In the small bowel 32 submucosa-intramural angiomas were found (1 in the distal jejunum was intussuscepting). Most of these gastrointestinal lesions were resected or tied off. Seven lesions were seen in the colon, but they were not treated. Since surgery, no further intestinal bleeding has occurred.

In some of the described cases in the literature, lesions in the nasal and urinary bladder mucosae have produced epistaxis and hematuria.—*J. B. Alvarez, M.D.*

Carswell, J. Wilson. Wandering spleen: 11 cases from Uganda. *Brit. J. Surg.*, June, 1974, *61*, 495–497. (From: Department of Surgery, Mulago Hospital, Kampala, Uganda.)

Eleven cases of wandering spleen are reported. Of the 11 cases, 6 presented with an abdominal mass known to be present between 2 and 6 years. These had been associated with chronic abdominal pain. Five patients presented with an acute abdomen and all were aware of an abdominal mass accompanied by vague discomfort for up to 8 years. The clinical diagnosis can be suspected if a hard abdominal mass with a notched border is palpated. The mass can be moved without pain towards the left hypochondrium, but with motion in every other direction causes pain and is limited in mobility. The left upper quadrant is resonant to percussion. One abdominal roentgeno-

gram described by the author demonstrated a mass in the left lower quadrant, with bowel under the entire leaf of the left hemidiaphragm.

In 1 patient, the diagnosis was made preoperatively, using Cr^{51} (2 c/kg.) and counting over the heart, liver and abdominal mass for 7 days. Since only 3 of the 11 cases in this series were over 10, the theory of traction by an enlarged spleen on its mesentery was questioned as the primary etiology. Two patients in the present series had mobile left colon attached to a short mesentery.

Since the spleen and colon both arise from the dorsal mesogastrium, the author postulates that a defect in the embryogenesis of the dorsal mesogastrium is responsible for both conditions.—*Ronald J. Ross, M.D.*

Genitourinary System

Enlander, Derek, Weber, Paul M., and dos Remedios, Leo V. Renal cortical imaging in 35 patients: superior quality with ^{99m}Tc-DMSA. *J. Nuclear Med.*, Sept., 1974, *15*, 743–749. (Address: Paul M. Weber, M.D., 280 W. MacArthur Boulevard, Oakland, Calif. 94611.)

The metal chelate dimercaptosuccinic acid will combine with technetium 99m in the presence of tin to form a radiopharmaceutical that localizes in the cortex of the kidney. The mean half time for plasma disappearance in 15 patients was 62 minutes, with only 6–9 per cent of the dose remaining in the blood at 14 hours. The cumulative renal excretion, determined in 5 patients, was 26–29 per cent at 24 hours. Quantification of renal concentration of the tracer revealed that 50 per cent of the injected dose was found in the kidneys at 1 hour, and a maximum concentration of 70 per cent occurs.

These renal concentrations of tracer permit the recording of extremely high quality scans, using magnifying collimators such as the pin hole.—*Wm. H. Strauss, M.D.*

Young, L. W., Wood, B. P., Spohr, C. H., and Panner, B. Delayed excretory urographic opacification, a puddling effect, in multicystic renal dysplasia. *Ann. de radiol.*, May–June, 1974, *17*, 391–396. (Address: L. W. Young, M.D., Departments of Radiology and Pathology, Strong Memorial Hospital, University of Rochester, Rochester, N. Y. 14642.)

Two cases of neonatal multicystic kidneys were diagnosed utilizing total body opacification with delayed roentgenograms.

Follow-up roentgenograms are obtained as late as 48 hours after injection. Delayed opacification of parenchyma around cysts or puddling of contrast medium within cysts is felt to be diagnostic of multicystic renal dysplasia. Such findings in intravenous urography would preclude the necessity for retrograde pyelography and cystoscopy.

The spectrum of multicystic renal dysplasia ranging from segmental to total involvement, with and without cysts, is discussed and correlation is made between radiologic and pathologic findings. The statement that "multicystic renal dysplasia can be excluded if the kidney is visualized on the IV Urogram" is refuted. Contrast material may "rim" and puddle within the cysts.—*Ronald J. Ross, M.D.*

Nervous System

André, J. M., Picard, L., Barrucand, D., and Kissel, P. Les manifestations neurologiques des polyposes digestives héréditaires. (The neurologic manifestations of hereditary digestive polyposes.) *Rev. Neurol.*, Dec., 1973, *129*, 325–338. (Address: J. M. André, Clinique Médicale B., C.H.U. de Nancy-Brabois, F 54500 Vandoeuvrelès-Nancy, France.)

Hereditary digestive polyposes are expressions of embryonic developmental abnormalities, principally of the endoderm. Thus familial, diffuse recto-colic adenomatous polyposes constitute the most frequent form, often discovered between ages of 20 and 30 and with high potential of malignant degeneration as compared to diffuse juvenile polyposes which are benign. When conjointly the ectoderm develops abnormally, nervous system involvements are noted such as Turcot's syndrome (intestinal polyposis and perioral lentigo associated less frequently with nervous manifestations). At times even abnormalitites of mesodermal origin can be observed as in Gardner's syndrome (osteomas, connective tissue tumors, recto-colic polyposis), Werner's syndrome (polyadenomatosis, gastric polyposis), and polyposes associated with osteomatosis or angiomatosis.

All these syndromes manifest the same functional symptomatology of diarrhea, recurring digestive tract hemorrhages and obstructions (often due to intussusception) and inanition and dehydration (specially infants). They are transmitted by a dominant autosomal modality.

The authors present 1 case of Turcot's syndrome, 1 case of Gardner's syndrome, 2 of Peutz-Jeghers syndrome, and 1 case of familial diffuse polyposis associated with external carotid (bilateral) angiomatosis and multiple subcutaneous tumors.—*Jirair N. Sarian, M.D.*

Pataro, Vincente F., and Conde, Rodolfo Martinez. Tumores presacros. (Presacral tumors.) *Prensa méd. argent.*, June, 1974, *61*, 473–482. (From: Policlinico "Ricardo Finochietto," Servicio de Clinica Quirúrgica, Avellaneda, Pcia de Buenos Aires, Argentina.)

Presacral tumors are rare. Most of them are congenital in nature. The authors report 4 such tumors.

The first case was a teratoma. The patient was a 17 year old girl who had a mass in the sacrococcygeal area since birth. This mass grew slowly. When examined the mass measured 15×15 cm. The radiologic examination showed displacement of the sacrum, but no destructive changes. This type of tumor can become malignant; therefore, surgery should be done as soon as possible, and the surgeon should excise the tumor completely. This patient was cured.

The second case was a dermoid. This patient was a 48 year old woman who had right leg pain for 9 years and rectal tenesmus for 3 months. The tumor was removed and the patient is cured.

The third case was a chordoma in a 49 year old woman, who had anal rectal pain for 5 years. The radiologic examination showed partial destruction of the sacrum and the coccyx. After surgery the symptoms disappeared for 1 year, but after that she had recurrence of the tumor and the pain. She has been treated with several courses of radiotherapy (cobalt). She also required a chordotomy. The patient is alive 10 years after the original surgery, but she still has a local tumor and has difficulty walking. It should be noted that this type of tumor frequently recurs locally, and sometimes metastasizes.

The fourth case was a lipomyxoma in a 39 year old man with a short history of a gluteal mass and anal pain and pruritus. The radiologic examination was unremarkable. A combined perineal-abdominal approach was necessary to excise the entire tumor.—*J. B. Alvarez, M.D.*

Wilson, L. M. Kinnier, and Draper, G. J. Neuroblastoma, its natural history and prognosis: a study of 487 cases. *Brit. M. J.*, Aug., 1974, *3*, 301–307. (From: The Research Department, Marie Curie Memorial Foundation and the Department of Social Medicine, Oxford University, Oxford, England.)

The natural history of neuroblastoma and factors affecting survival were studied in an unselected group of children reported to the cancer registries in Britain from 1962–1967. A 3 year survival rate based on 487 cases was 23 per cent. There were only 5 deaths among 110 cases followed for more than 3 years and approximately two-thirds of those for more than 5 years.

The factors affecting prognosis included: age at diagnosis; site; histologic grade at diagnosis; and sex. Interrelationshlp between these factors and prognosis was analyzed. Apparently girls have a significantly better survival rate than boys and histologic evidence supports the suggestion that the likelihood of maturation for neuroblastoma is greater for girls than for boys. These patients were below the age of 15 at the time of diagnosis.

The Willis classification by histologic findings was into 5 main categories; 1. the undifferentiated round cell malignant tumor; 2. the early differentiated group; 3. the unspecified group; 4. the ganglioneuroblastomas; and 5. the mature ganglioneuromas.

The sites of distribution within the abdomen are adrenal and extra-adrenal including those arising from the lumbar sympathetic chain and associated ganglia.

Thoracic sites comprised 2 groups: those tumors which were described during surgery as arising from the ganglia and were therefore presumably earlier tumors; and the remainder of the thoracic tumors whose origins were not clearly definable.

Neuroblastomas arising in liver formed a second group and many of these had exploratory laparotomies showing no primary deposit anywhere else. It has been suggested that they arise from abnormal distribution of neural crest cells.

For staging, the method of Evans was used: Stage I tumor confined to organ or structure of origin; Stage II tumor extending in continuity beyond the organ or structure of origin, but not crossing midline and regional lymph nodes on the homolateral side possibly involved; Stage III tumor extending in continuity beyond the midline and regional lymph nodes involved bilaterally; Stage IV remote disease involving skeleton, organs, soft tissue, or distant lymph nodes; and Stage IV-S cases who would be otherwise a Stage I or II but who had remote disease confined only to one or more of the following sites: liver, skin, or bone marrow without bone metastases.

History and symptoms are quite variable depending upon age of the patient and site of diagnosis.

The discussion involves a good summary, indicating that neuroblastoma is the third commonest neoplasm among children exceeded only by leukemia and cerebral tumors. Maturation from malignant undifferentiated neuroblastoma to benign ganglioneuroma is a noteworthy feature. The over-all better survival rate of extra-adrenal *versus* adrenal neuroblastoma is corroborated.—*Lionel W. Young, M.D.*

Blood and Lymph System

Bouhoutsos, John, and Martin, Peter. Popliteal aneurysm: a review of 116 cases. *Brit. J. Surg.*, June, 1974, *61*, 469–475. (From: Royal Postgraduate Medical School and Chelmsford Hospitals, Chelmsford, England.)

The clinical presentations, anatomy and treatment of 116 popliteal aneurysms occurring in 84 patients were reviewed retrospectively. Atherosclerosis was the etiologic factor in 102 of the aneurysms. Intermittent claudication, an associated abdominal aortic aneurysm or distal gangrene from embolism were frequent coexisting conditions. Thrombus of the aneurysm occurred acutely or was present at the

time of study in two-thirds of the cases. Nerve pressure, rupture or acute infection was not seen.

Angiography usually demonstrated the aneurysms when patent, but in some, laminated thrombus lining the aneurysm precluded visualization. A variety of bypass procedures was used to treat the aneurysms and in some patients amputation was required.

The authors conclude that angiographic examination of both extremities should be considered because of the increased incidence of asymptomatic popliteal aneurysm on the uninvolved side. The prognosis after surgical therapy was similar to patients with abdominal aortic aneurysm or intermittent claudication alone.—*Robert I. White, Jr., M.D.*

Skeletal System

Epstein, Herman C. Posterior fracture-dislocations of the hip: long-term follow-up. *J. Bone & Joint Surg.*, Sept., 1974, *56-A*, 1103–1127. (Address: 10450 Wilshire Boulevard, Apartment 7, Los Angeles, Calif. 90024.)

Long term results after posterior fracture dislocations of the hip, treated by closed reduction, closed reduction followed by an open procedure, and primary open reduction were reviewed in 599 traumatic dislocations and fracture dislocations treated at Los Angeles County—University of Southern California Medical Center between 1928 and 1970.

Patients followed for less than 1 year who had good results were not included, but all patients with fair or poor results were included. Of 242 patients suitable for analysis, 150 patients were followed for from 4 to 27 years. Of 242, 112 were treated by closed reduction, 74 by closed reduction followed by open procedure, and 56 by primary open reduction.

For the purpose of correlating results with the type of fracture-dislocation the cases were classified according to Thompson and Epstein's 5 types of posterior dislocations, and results of the different methods of treatment were analyzed in each group.

In 11 hips, in which open reduction was performed through an anterior approach, there were no good results. Results in the series were better after primary open reduction than after operation performed as a sequel to closed reduction. In the 35 Type III fracture-dislocations treated by closed reduction there was only 1 good result after a follow-up of 9½ years, whereas in 25 patients treated by primary open reduction, there were 17 good results. Scrupulous removal of loose fragments, many of which cannot be recognized on roentgenograms, is an important factor in the good results.

Type IV fracture-dislocations have poor results because of the disruption of the acetabulum. In this group good results were obtained in 5 of 38 closed reductions, 5 of 12 treated by open reduction following closed reduction, and 6 of 14 treated by primary open reduction.

The superiority of primary open reduction with removal of loose fragments was particularly striking in Type V cases, where there were no good results after closed reduction, 31 per cent good results after open reduction following closed reduction, and 56 per cent good results after primary open reduction. The lesser head fragment should be removed if it does not contain too much head.

It was evident that the initial result 1 year after reduction seldom improved. Only 8 of the 42 hips followed more than 10 years showed evidence of traumatic arthritis developing as a late complication. The best results occurred in hips in which the dislocation was reduced less than 24 hours after injury.

It was of interest that none of the patients were wearing seat belts at the time of the accident. All but 2 of the fracture dislocations occurring as a result of automobile accidents were the result of the knee striking the dashboard and could have been prevented by a seat belt.—*Lois Cowan Collins, M.D.*

Mabille, J.-P., Benoit, J.-P., and Castera, D. Dysplasie métaphysaire de Pyle. (Pyle's metaphyseal dysplasia.) *Ann. de radiol.*, Nov.–Dec., 1973, *16*, 723–730. (Address: J.-P. Mabille, Service de Radiologie de l'Hôpital du Bocage, C.H.U. de Dijon, F. 21000 Dijon, France.)

Clinical symptomatology and roentgen study of metaphyseal dysplasia was first described by Edwin Pyle in 1931.

A 54 year old female patient radiographed for a recent fracture of the upper part of the femur led the authors to discover the condition from the roentgen findings of the pelvis. Fine roentgenograms are presented which demonstrate the typical deformities. There is widening of ischial rami with narrowing of obturator foramina. The long bones show more striking changes; widening of the metaphyseal region to mid diaphysis gives the appearance of an elongated Erlenmeyer flask to the femur. Mild expansion of femoral necks with discrete coxa valga is noted. The tibial mid diaphysis shows slight S type of curving with cortical thickening. Bilateral genu valgum is also noted. The short tubular bones, the ribs, the clavicles, the mandibles and at times even the vertebrae show this pseudo-expansion. The skull roentgenograms demonstrate mild osteosclerosis of the cranial vault with moderate petrous pyramids of the temporal bones and lack of pneumatization of mastoids. Supraorbital prominence, some hypoplasia of paranasal sinuses and expansion of the ascending rami of mandible are also noted. These roentgen changes of cranium in Pyle's dysplasia when contrasted with marked osteosclerosis and deformity of skull and facial bones as noted in the craniometaphyseal dysplasia of Jackson, constitute some of the important differential diagnostic points between the 2 diseases.

Also, Jackson's dysplasia is progressive and at times lethal, whereas Pyle's is benign. On the other hand, the differential diagnosis between Jackson's dysplasia and Albers-Schönberg disease is at times difficult; however, the latter shows more marked osteosclerotic changes of the skull and vertebral involvement.—*Jirair N. Sarian, M.D.*

Bleifeld, Charles J., and Inglis, Allan E. The hand in systemic lupus erythematosus. *J. Bone & Joint Surg.*, Sept., 1974, *56-A*, 1207–1215. (Address: Charles J. Bleifeld, M.D., 111 Sheppard Street, Victorville, Calif. 92392.)

Involvement of the musculoskeletal system is the most frequent presenting complaint, with subjective complaints outweighing the objective findings. Detailed examination of the hands of 50 patients with documented lupus erythematosus (46 females and 4 males, average age 35.6 years), of which 37 had roentgenograms of the hands, form the basis for the report.

Raynaud's phenomenon was the most serious subjective complaint and was present in 50 per cent of patients. Joint pain was present in 75 per cent, but was usually mild. Joint swelling was present in 65 per cent, often only at the onset of disease when synovitis and joint effusions were severe. Almost all of the patients were on corticosteroids which controlled symptoms very well.

Sensory alterations, particularly a loss of fine touch, were present in 24 per cent.

Generalized ligamentous laxity, present in 50 per cent, caused deformities, particularly lateral instability of the distal interphalangeal joints, and swan neck deformities of several fingers. The proximal interphalangeal joints could always be fully flexed even with the metacarpophalangeal joints in extension. Even when the deformity was of long duration, the roentgenograms showed no articular destruction.

Hyperextension of the interphalangeal joint of the thumb was seen in 30 per cent, and was never associated with a flexion deformity of the first metacarpophalangeal joint. This joint could be subluxated in 16 per cent, but the joint remained aligned during hand function, and was normal roentgenographically.

Ulnar deviation was present in 14 per cent, but always reversible. The skin was usually tight, but overall vascularity appeared adequate except during acute attacks of Raynaud's phenomenon.

Roentgenograms were notable principally for their normal appearance. Juxta-articular osteoporosis was noted in 20 per cent. Periarticular calcification was present in 4 patients. Small subchondral cysts were seen in 2, 1 of whom had severe osteonecrosis of femoral heads and medial femoral condyles. He had been on large doses of corticosteroid and the joint changes were felt to be secondary to the osteonecrosis.

The authors feel that the involvement in systemic lupus erythematosus differs from rheumatoid arthritis by (1) absence of repeated attacks of acute synovitis with progressive deformity; (2) rapid improvement on corticosteroid therapy; (3) frequent presence of Raynaud's phenomenon (which is resistant to corticosteroid therapy); (4) absence of ankylosis in joint deformities, and absence of functional disability; and (5) absence of roentgenographic evidence of joint destruction.

Swan neck and thumb hyperextension deformities with intact joint spaces are characteristic of lupus. Periarticular calcification occurs occasionally but is not specific.—*Lois Cowan Collins, M.D.*

Ring, Ernest J., Waltman, Arthur C., Athanasoulis, Christos, Smith, James C., Jr., and Baum, Stanley. Angiography in pelvic trauma. *Surg., Gynec. & Obst.*, Sept., 1974, *139*, 375–380. (From: The Departments of Radiology, Harvard Medical School and Massachusetts General Hospital, Boston, Mass.)

The authors percutaneously catheterized the lower abdominal arterial and venous trunks to delineate the nature and extent of vascular injury following pelvic trauma, and to plug leaking arteries by an ingenious technique: intraarterial injection of autologous clotted blood.

Arteriography was performed after positioning the catheter tip above the bifurcation of the aorta, *via* the femoral artery on the less injured side, or utilizing an axillary artery approach. The hypogastric artery was cannulated by advancing the catheter tip across the aortic bifurcation. After identification of bleeding points, 2 to 3 ml. of autologous blood clot mixed with 10 ml. of contrast agent was injected selectively to occlude the bleeding site. If coagulation deficiencies related to multiple blood transfusions precluded spontaneous clotting, thrombin was added to the patient's blood, forming a stable clot rapidly. Extreme care was exercised to position the catheter tip well within the internal iliac artery to avoid embolization into the leg. Hemostasis of a laceration too large for effective embolization was accomplished by inflating a Fogerty catheter proximally. Eight of 12 patients were successfully treated; 1 required subsequent surgical evacuation of a pelvic hematoma; 3 died.

Post-traumatic arteriovenous fistulas have been treated with embolization utilizing autologous blood clot, muscle fragments, or Gelfoam. However, extreme caution was exercised in employing this technique; there is the danger of pulmonary embolization should the occluding bolus cross the arteriovenous communication.

Arteriography delineated pelvic arterial occlusions, resulting from compression by adjacent hematoma, thrombosis, spasm, or pre-existing arteriosclerosis.

Establishing the extent of the block and the collateral pathways facilitated surgical management of the patient. Similarly, post-traumatic pseudoaneurysms were identified.

If no arterial bleeding site was found, if blood loss continued after occlusion of arterial bleeders, or if venous thrombosis was suspected, percutaneous femoral (catheter) venography was performed to evaluate injury to the iliac veins or their tributaries. Venous lacerations were repaired surgically.

Sixty per cent of deaths following pelvic trauma have been attributed to massive extraperitoneal hemorrhage. Angiography was performed rapidly, and did not interfere with other resuscitative measures. As indicated, the procedure was extended to assess concurrent injuries to organs such as the kidneys, liver, spleen, or brain.—*Adele R. Altman, M.D.*

Resnick, Donald. Rheumatoid arthritis of the wrist: why the ulnar styloid? *Radiology*, July, 1974, *112*, 29–35. (Address: Department of Radiology, Veterans Administration Hospital, 3350 La Jolla Village Drive, San Diego, Calif. 92161.)

Swelling and erosive abnormalities about the ulnar styloid are characteristic early changes of rheumatoid involvement of the wrist. To better define the pathogenesis of changes about the ulnar styloid, the author studied wrist roentgenograms in 100 rheumatoid patients, wrist arthrograms in 20, surgical pathologic sections in 10, gross and microscopic sections from 20 "control" and rheumatoid cadavers, and arthrograms in 6 rheumatoid cadavers.

It is important to understand the anatomic features of the wrist in order to appreciate the pathologic changes. Of particular importance are: (1) the radiocarpal joint with its prestyloid recess; (2) the inferior radioulnar compartment; and (3) the sheath and tendon of the extensor carpi ulnaris.

The prestyloid recess of the radiocarpal joint is immediately adjacent to the anterior surface of the ulnar styloid or may entirely surround it. The inferior radioulnar compartment is an L-shaped recess lying between the head of the ulna and the ulnar notch of the radius. It is normally separated from the radiocarpal compartment by the triangular cartilage. The sheath and tendon of the extensor carpi ulnaris lie adjacent to the posterior aspect of the head of the ulna.

This last site may be where the earliest changes of rheumatoid involvement of the wrist occur. Tendinitis and tenovaginitis result in proliferative synovitis and production of edematous granulation tissue. Erosions along the outer margins of the ulnar styloid may be due to involvement of this tendon sheath. Soft tissue swelling over the medial head of the ulna is due to synovial overgrowth around the extensor carpi ulnaris tendon. Erosions at the tip of the ulnar styloid are due to abnormal synovium in the prestyloid recess. Erosions of the radial and volar surfaces of the distal ulna are due to involvement of the inferior radioulnar compartment. Focal periostitis frequently seen along the outer distal margins of the radius and ulna may be due to attempts at healing of eroded bone.—*J. M. Staebner, M.D.*

McLennan, Thomas W., and Steinbach, Howard L. Shwachman's syndrome: the broad spectrum of bony abnormalities. *Radiology*, July, 1974, *112*, 167–173. (Address: Thomas W. McLennan, M.D., Department of Radiology, Stanford University Medical Center, Stanford, Calif. 94305.)

The Shwachman syndrome, as originally described, consisted of: diarrhea; failure to thrive; exocrine pancreatic insufficiency; neutropenia associated with bone marrow hypoplasia; elevation of fetal hemoglobin; inconstant galactosuria; and growth retardation.

Exocrine pancreatic insufficiency is probably congenital, often manifesting itself in infancy with diarrhea or steatorrhea and failure to thrive. Cystic fibrosis is excluded by normal sweat electrolyte concentrations and absence of characteristic respiratory tract infections. The hematologic picture may be dominated by a constant and severe ($<1{,}000/mm.^3$) neutropenia, although it has been rare or cyclic in reported cases. Hypoplastic anemia and thrombocytopenia occur less frequently, but may be especially severe.

Recurrent upper and lower respiratory infections, sinusitis, and skin infections develop, characteristically unrelated to the severity of the neutropenia. Generalized immunoglobulin deficiencies are usually present.

Retardation of growth is a frequent feature of the syndrome, dwarfism being present in at least a third of 45 similar cases reported in the world literature.

Eleven of 45 cases of Shwachman's syndrome previously reported exhibited what is recognized by radiologists as metaphyseal chondrodysplasia (cupping and defective irregular mineralization of the epiphyseal cartilage with normal laboratory values for calcium and phosphorus). The metaphyseal irregularities may be isolated. More generalized metaphyseal chondrodysplasia and bone deformity with especially severe structural changes in the hips have been reported. The relationship of the bone changes to Shwachman's syndrome, especially the inconstantly associated physeal dysplasia remains unclear.

Two new cases of Shwachman's syndrome are reported and previous reports reviewed to illustrate the wide range of osseous abnormalities associated with the syndrome of pancreatic exocrine unsufficiency and bone marrow dysfunction. Early radiographic recognition of the bone abnormalities of Shwachman's syndrome may facilitate diagnosis and prediction of the other diverse manifestations of the serious disorder.—*Jon F. Bergstrom, M.D.*

General

Akbarnia, Behrooz, Torg, Joseph S., Kirkpatrick, John, and Sussman, Sidney. Manifestations of the battered-child syndrome. *J. Bone & Joint Surg.*, Sept., 1974, *56-A*, 1159–1166. (From: The Departments of Orthopedic Surgery, Radiology, and Pediatrics, St. Christopher's Hospital for Children, Philadelphia, Penn.)

In a study of 231 children with the battered-child syndrome admitted to St. Christopher's Hospital for children in Philadelphia, Pa., between 1965 and 1972, 34 per cent (74 patients) required orthopedic treatment. Approximately 50 per cent were less than 1 year old, and 78 per cent less than 3. The 74 children with fractures averaged 3.6 fractures per child (range 1 to 15 fractures). In decreasing order of frequency, distribution was as follows: ribs—72; humerus—42; femur—32; tibia—31; skull—25; hand—15; ulna—12; radius—11; others—24.

The history of trauma in these patients usually is lacking, but the physician should be alerted to its possibility by various skin lesions, such as ecchymoses, burns, welts, lacerations and scars. Failure to thrive or growth retardation secondary to physical and emotional deprivation was observed in 4 patients. The majority of fractures occurred in infants, an age group in which fractures are infrequent. Seventeen infants had skull fractures and a number had inappropriate widening of sutures thought to be due to cerebral edema or subdural hematoma.

The bone lesions were classified as follows:

A. Metaphyseal: (1) Impactions; (2) buckle fractures; (3) irregular metaphyseal deformity; (4) periosteal avulsion.
B. Diaphyseal: (1) Exuberant callus; (2) multiple lesions in varying stages of healing; (3) gross deformity.
C. Miscellaneous: (1) Skull fracture with widened sutures; (2) multiple rib fractures; (3) thoracolumbar spine lesions.

Several of these injuries are particularly suggestive of battered-child syndrome. Symmetric periosteal new-bone formation secondary to metaphyseal avulsion and periosteal hemorrhage may not be evident when the child is seen initially with painful and swollen extremities, but becomes apparent a week or 2 later. Exuberant callus at diaphyseal fractures is probably due to lack of immobilization. Multiple fractures in different stages of healing are probably one of the most suggestive findings.

When a physician encounters any of the evidences which suggest the battered-child syndrome, he should take the following steps to protect the child:

1. Admit the child to the hospital immediately, if for no other reason than to protect the child from further battering.
2. Submit a report of suspected child abuse to the appropriate agency within 48 hours.
3. Order appropriate pediatric, neurosurgical, ophthalmologic and general surgical consultations where indicated.
4. Order a skeletal survey to determine other evidence of recent or past injury to bones.

Such action may save a child from permanent injuries or even death due to continued beatings.—*Lois Cowan Collins, M.D.*

RADIATION THERAPY

Fenner, Matthew L. The treatment of primary breast cancer by radical radiotherapy with artificial pneumothorax. *Clin. Radiol.*, April, 1974, *25*, 203–210. (From: Plymouth and Cornwall Radiotherapy Centre, Freedom Fields Hospital, Plymouth, England.)

From a survey of the literature, the author concludes that breast carcinoma is fundamentally one of 2 different diseases. One is a cancer which spreads principally by lymphatics and in which, if hematogenous spread occurs, the mortality of the tumor emboli is so high that the cancer is still curable by local means. The other disease is disseminated from the outset and no local treatment will affect it. In addition, he finds little choice among the various types and combinations of current therapy, particularly in the influence upon long term prognosis.

Therefore, he has devised a new means of administering radiotherapy, directed toward the pathways of lymphatic spread, as an alternative to surgical treatment. The treatment is directed not only toward the primary tumor, but toward the internal mammary lymphatic chain, the supraclavicular fossa, and the axilla. Since the possibility of damaging the lungs by irradiation was the principal reason for withholding treatment to all these regions in the past, the author has induced artificial pneumothorax to prevent pulmonary damage, while treating the lymphatic structures adequately.

In practice, all patients with breast carcinomas of Stage I, II, or III in whom a pneumothorax can be safely induced are treated with radical radiotherapy. A mold is prepared in which the location of the axillary, internal mammary, and supraclavicular lymph nodes is indicated. After complete pneumothorax has been induced over a period of a week, a total minimum tumor dose of 5,720 roentgens in 22 fractions is administered. Following this, the lung is allowed to re-expand slowly. Occasionally, additional air must be injected during the treatment to maintain lung collapse. Sometimes pleural fluid appears, presumably due to bleeding from the manipulation, and rarely slight pleural fibrosis develops.

In 2 cases out of 53 treated, a residual mass was palpable in the breast, and since mammography suggested residual tumor, both patients were treated by simple mastectomy 2 or 3 months after irradiation.

There was no operative difficulty or delay in healing.

This method permits irradiation of the entire chest wall avoiding both the morbidity of overlapping fields and the recurrence risk of a nonirradiated field as well as the complications inherent in irradiation of the lung, heart and esophagus. This technique will not influence the incidence of generalized metastases in those patients whose disease is already disseminated, but a dramatic reduction in the incidence of delayed recurrence is anticipated, especially in those patients in whom chest wall metastases, pleural effusion, or thoracic vertebral metastases might otherwise occur.—*E. Frederick Lang, M.D.*

Singhakowinta, Amnuay, Henderson, Michael D., and Vaitkevicius, V. K. Bilateral adrenalectomy in selected patients with carcinoma of the breast. *Surg., Gynec. & Obst.*, May, 1974, *138*, 689–692. (From: The Division of Oncology, Wayne State University School of Medicine and the Milton A. Darling Memorial Center of the Michigan Cancer Foundation, The Grace Hospital, Detroit, Mich. 48201.)

Carcinoma of the breast is the most common malignant tumor of females in this country and in more than half of these women, disease eventually becomes disseminated. Several forms of therapy have proved beneficial for patients with disseminated disease and include chemotherapy, therapeutic castration, hormonal therapy, hypophysectomy, and bilateral adrenalectomy.

The authors review a group of 26 patients selected for bilateral adrenalectomy at Wayne State University, School of Medicine.

Recommendation for ablative adrenal surgery was made at that institution only in those patients who had clearly shown evidence of hormonally dependent tumors. Convincing hormonal dependence of the tumor could be demonstrated in 1 of 3 ways.

(1) Response to oophorectomy. Oophorectomy was the first therapeutic procedure used in the premenopausal category. If there was objective evidence of response to this procedure, the patient would be considered for subsequent bilateral adrenalectomy.

Category (2) was a group of postmenopausal women who responded to large doses of estrogen with a hypercalcemic flare. If calcium elevation occurs in response to estrogen administration, it is implied that there has been a sudden rapid progression of tumor within the bone. This is considered an evidence of hormonally dependent tumor. Bilateral adrenalectomy in selected patients with carcinoma of the breast is performed.

(3) "Hormonal withdrawal regression." In patients receiving estrogen without evidence of hypercalcemia, hormone therapy was continued until the disease progressed. At this point, the hormone was discontinued and then patients were observed for sudden tumor regression.

Of the 26 patients in the category of hormonally dependent tumor, who were subjected to bilateral adrenalectomy, 20 patients responded. The authors point out that this is an unusually high response rate and attribute this to the specificity of the selection process. This process of selection excludes a significant number of patients who might have responded to adrenalectomy, but in whom the probability of response was lower.

Laboratory tests are badly needed to predict hormonal dependent tumors in order to supplement clinical criteria for patient selection.—*R. H. Troupin M.D.*

St. Louis, Eugene L., McLoughlin, Michael J., and Wortzman, George. Chronic damage to medium and large arteries following irradiation. *J. Canad. A. Radiologists*, June 1974, *25*, 94–104. (Address: Eugene L. St Louis, M.D., Department of Radiology The Wellesley Hospital, Toronto, Ontario Canada.)

Radiation injury to small vessels is well documented both in man and the experimental animal. Large and medium sized arteries are far less sensitive to external radiation, but changes have been demonstrated on experimental animals.

The authors present 7 patients with chronic radiation damage to elastic arteries demonstrated by angiography. Chronic radiation damage may include (1) Ischemic necrosis secondary to narrowing or occlusion of vasa vasorum producing loss of elastic tissue and muscle fibers, followed by replacement fibrosis; (2) adventitial and periadventitial fibrosis producing obstruction; (3) acceleration of development of atherosclerosis.

Radiation dosage in reported cases ranges from 1,440 r to 11,000 r. Little detail is available and there is insufficient information to draw conclusions regarding time-dose relationships. The time of onset of symptoms after initiation of irradiation ranged from 2 months to 39 years with a mean time of 12.6 years. Because of this long latent period before development of signs and symptoms of arterial insufficiency the relative contribution of advancing age in the patient, as compared with the effect of radiation therapy, is sometimes difficult to evaluate. Mark involvement of vessels by the disease process was localized to the former treatment area is considered good evidence for a radiation effect.

Three cases are reviewed in which radiation therapy was administered for "benign lesions." An 8 year old female received irradiation for "tonsilitis" and died at age 38, with autopsy findings of total occlusion of both common carotid arteries. A patient in his first decade of life had repeated radiotherapy for laryngeal papillomata and was shown angiograph

cally, at age 37, to have complete occlusion of both common carotid arteries. A young male received repeated irradiation for a similar disorder, and 24 years later was shown to have complete occlusion of the left common carotid artery and severe stenosis of the right.—*David Morse, M.D.*

Abramson, Norman, Ornitz, Robert, and Cavanaugh, P. J. The effect of local irradiation on rejection of the transplanted kidney. *Radiology*, Aug., 1974, *112*, 413–416. (Address: Norman Abramson, M.D., Division of Radiation Therapy, Duke University Medical Center, Durham, N. C. 27710.)

In the field of renal transplantation, rejection of the organ still remains the major obstacle to success. Renal rejection is a complex process involving both cell-mediated and humoral antibody response. Simply stated, there are antigens on the surface of the donor's kidney cells which are recognized as being foreign to the recipient's immune surveillance system. Thus, following transplantation, a local immune reaction occurs which results in disruption of the membranes of the endothelial cells of small intratubular vessels causing extravasation of red blood cells. Intravascular coagulation follows and produces acute tubular necrosis and renal failure. Rejection can be detected by alterations in laboratory values which reflect kidney function (blood urea nitrogen, creatinine clearance, and urine output). Various methods are used to combat rejection. These include Imuran, steroids, antilymphocyte globulin, and irradiation (whole body, extracorporeal, intralymphatic and local). Of all of these, local irradiation is the most popular. It apparently is effective because it directly kills immunocytes and thus slows or stops the rejection phenomenon.

This paper is a report of the experience at Duke University Medical Center and affiliated Durham Veterans Administration Hospital on the use of local irradiation to prevent rejection following transplantation. Between 1965 and 1973, 174 renal transplantations were performed. Of these, 54 patients were referred for local irradiation in an attempt to halt rejection. Forty patients were male and 14 female; 32 received cadaveri kidneys and 22 received transplants from either a parent or a sibling; and 10 were irradiated twice. Following transplantation, all patients were placed on steroids and Imuran. Chemical tests monitored their progress. If rejection developed, usually within 24–48 hours, additional high doses of steroids and antilymphocyte globulin were added in some cases. Then radiation was delivered through a single anterior portal, the dose usually being 900 rads in 6 fractions every other day. If rejection continued, an additional 600 rads was added in 4 fractions.

The results showed that one-third of patients referred for irradiation survived 3 to 54 months, suggesting that the rejection phenomenon was reversed or at least modified by the irradiation. A dose-response relationship could not be established, however.

It was concluded that until there is a clearer understanding of the rejection phenomenon itself and the methods of its reversal, continued use of irradiation of the transplanted kidney should be recommended when signs of rejection occur.—*Paul M. Kroening, M.D.*

RADIOISOTOPES

Nishiyama, H., Sodd, V. J., Berke, R. A., and Saenger, E. L. Evaluation of clinical value of ^{123}I and ^{131}I in thyroid disease. *J. Nuclear Med.*, April, 1974, *15*, 261–265. (Address: H. Nishiyama, Nuclear Medicine Laboratory, Cincinnati General Hospital, Cincinnati, Ohio 45229.)

The authors summarize their comparison of I^{123} and I^{131} for thyroid uptake and scans in 24 patients. The iodine 123 was produced by alpha bombardment of a tellurium 122 target to produce xenon 123 which decays to iodine 123. The radionuclidic purity of this preparation was 99.7 per cent as determined by gamma ray spectroscopy.

The authors found no significant difference in uptake values. The scans were interpreted by a panel of 6 physicians who rated scans performed with iodine 123 to be superior in 78 per cent of the studies. The majority thought that scans obtained with a low energy collimator were superior to those obtained with a fine focus collimator used principally for the iodine 131 scans.

Using 100 microcuries of the high quality iodine 123, the average thyroid dose was 2.73 rads and the whole body dose 0.0095 rads. By comparison, a similar dose of iodine 131 produced a thyroid dose of 210 rads and a whole body dose of 0.36 rads.—*Merle K. Loken, M.D., Ph.D.*

Nebesar, Robert A., Rabinov, Keith R., and Potsaid, Majic S. Radionuclide imaging of the spleen in suspected splenic injury. *Radiology*, March, 1974, *110*, 609–614. (Address: Robert A. Nebesar, M.D., Department of Nuclear Medicine, Cardinal Cushing General Hospital, 235 N. Pearl Street, Brockton, Mass. 02401.)

In cases of blunt abdominal trauma resulting in splenic injury, the diagnosis may be clearly defined by physical examination and routine abdominal roentgenograms, or the diagnosis may be very difficult to establish. In the latter cases, splenic angiography has been advocated. Others have demonstrated ruptured spleens by radionuclide imaging, but the accuracy of this has not been established. Neither has a valid comparison with angiography been done.

Radiocolloid splenography in 32 patients suffering blunt abdominal trauma is reported, and angiographic comparisons are made where possible.

A dose of 1–4 millicuries of Tc^{99m} sulfur colloid was administered intravenously, and imaging begun 15–30 minutes later. Dosage was based on age and weight. Multiple images were obtained of the spleen: anterior, left anterior oblique, left lateral, left posterior oblique, and posterior. Right anterior oblique, right posterior oblique, cephalad, or caudad angled images were obtained when deemed necessary. Liver images were obtained in most instances. Most studies were done as emergencies, and completed within 1 hour. Ten of the 32 patients so studied also received selected celiac and/or splenic angiography.

The radiocolloid image abnormalities were classified as linear, wedge-shaped, stellate, or concave. Linear or stellate defects were thought more specific, and the others were thought to be less specific. The defects were mostly marginal, extending inward, although central defects were seen.

Thirteen cases were declared abnormal, and operation confirmed splenic rupture in 11 cases. The other 2 stabilized and never came to surgery. Three cases were called equivocal, were never operated, and all 3 recovered. Sixteen were read as normal. Three of these were operated, but only 1 was found to have splenic injury. The other 13 "normals" recovered clinically.

Of the 10 angiograms, 9 were technically satisfactory for interpretation. Six of the 9 correlated with radiocolloid interpretation. These were those read as either positive or negative. Three angiograms were read as equivocal. One of these patients carried a positive reading or radiocolloid imaging, but was not explored, and remained well. One patient was also a radiocolloid equivocal, was not explored, and remained well. The other patient was the negative radiocolloid image, in whom splenic injury was found at surgery.

This study suggests a possible 90 per cent accuracy rate by radiocolloid imaging of the spleen. However, it must be remembered that the procedure is nonspecific. Angiography is more specific when extravasation is seen, but this is not always present.

On the basis of sensitivity, radiation exposure, procedural risk, and cost, radiocolloid splenography should be considered as the primary "special radiological technique" in the diagnosis of splenic trauma. When angiography is the procedure of choice because of possible injury to other intra-abdominal organs, *e.g.*, kidneys, radionuclide imaging may still be done as a preliminary "survey."—*F. C. Petty, M.D.*

MISCELLANEOUS

Henry, Robert E., Fletcher, James W., Solaric-George, Erica, and Donati, Robert M. Effect of granulocytopenia, marrow suppressive drugs, and infection on marrow reticuloendothelial patterns. *J. Nuclear Med.* May, 1974, *15*, 343–348. (Address: Robert E Henry, M.D., (172-JC), St. Louis VA Hospital, St. Louis, Mo. 63125.)

This study was done to determine whether th marrow pattern obtained with radiocolloid woul provide information about hematopoietic function i patients with Hodgkin's disease or lymphoma, wh had undergone extensive radiotherapy or treatmen with combinations of marrow toxic drugs.

Radiocolloids have been used to show the spati distribution of bone marrow.

The study comprised 26 patients with Hodgkin disease or lymphoma, and 24 patients including thos with acute pulmonary infections, renal transplan on immunosuppression therapy, adenocarcinoma pa tients receiving chemotherapy, and patients wit idiopathic granulocytopenia.

Each patient was given 3 millicuries of Tc^{99} sulfur colloid intravenously and liver, spleen an skeletal imaging was done using a gamma camer Marrow patterns were not considered to be extende if the activity was limited to the axial skeleton wit or without activity in the proximal one-fourth of th humerus and femur. Marrow patterns were co sidered to be extended, if there was activity beyon the proximal one-third of the humerus or femur.

Bone marrow extension was found in those cas of Hodgkin's disease or lymphoma, who had be treated with radiation, chemotherapy or a combin tion of both and in whom there was an associat granulocytopenia. There was a similar association those cases of renal transplants and metastatic ca cinoma rendered granulocytopenic by immun suppression or chemotherapy. The cases with gran locytopenia not associated with chemotherapy d not have marrow extension. Seven cases with acu bacterial infection and no primary hematologic d ease showed an extended marrow pattern.

Serial studies in patients with Hodgkin's disease lymphoma showed an association between the e tending reticuloendothelial marrow pattern and i tolerance to chemotherapy.

The above findings suggest that the reticu endothelial marrow extension following chem therapy and irradiation is due to compromis hematopoiesis reflected by granulocytopenia. T appearance of the reticuloendothelial marrow ext sion pattern following chemotherapy appears to dicate poor tolerance to further chemotherapy. T converse indicates an adequate marrow granulocy reserve.

Subclinical infections cannot entirely be excluc as a cause of reticuloendothelial marrow extension patients on chemotherapy with an associated gra locytopenia.—*Charles W. Cooley, M.D.*

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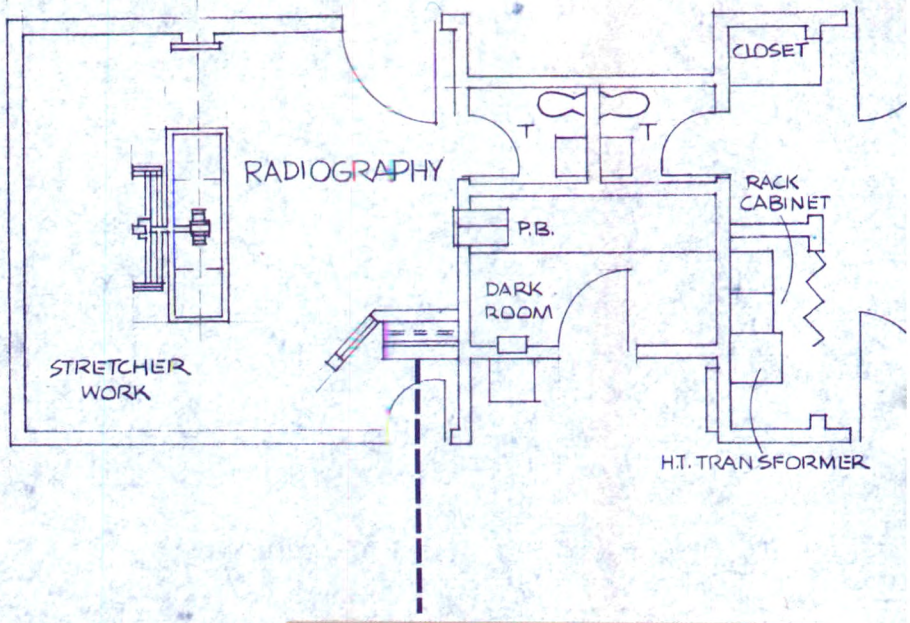

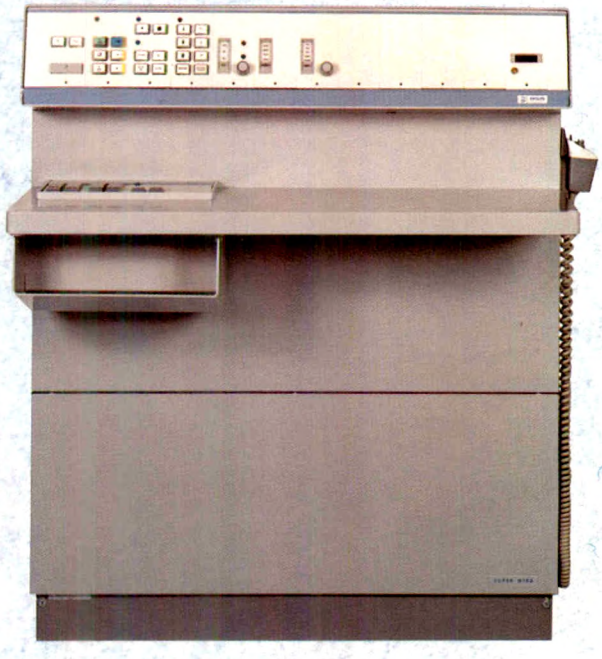

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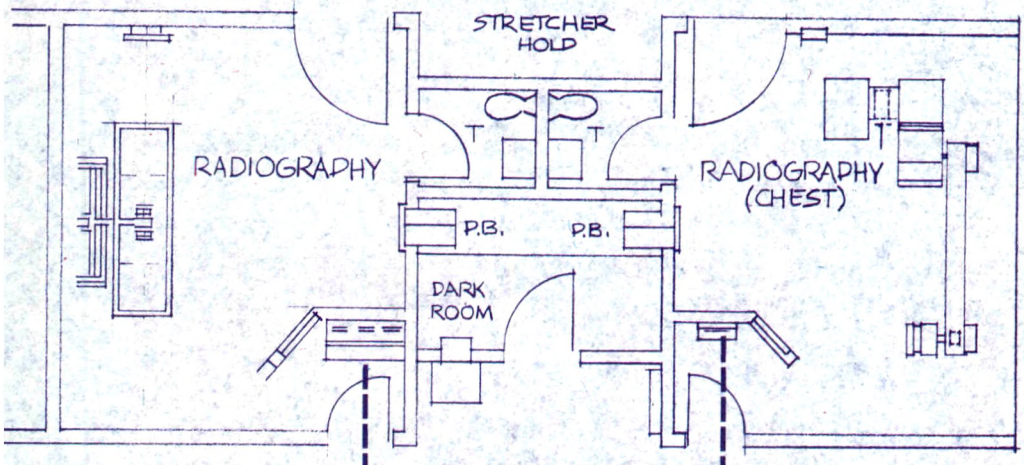

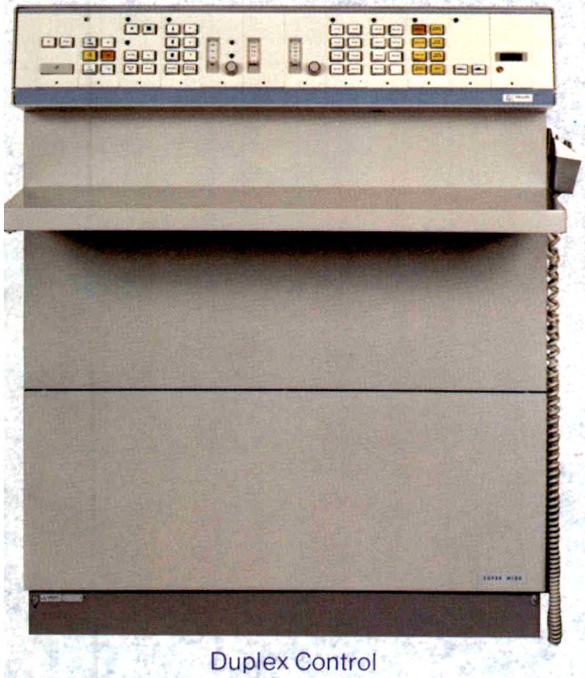

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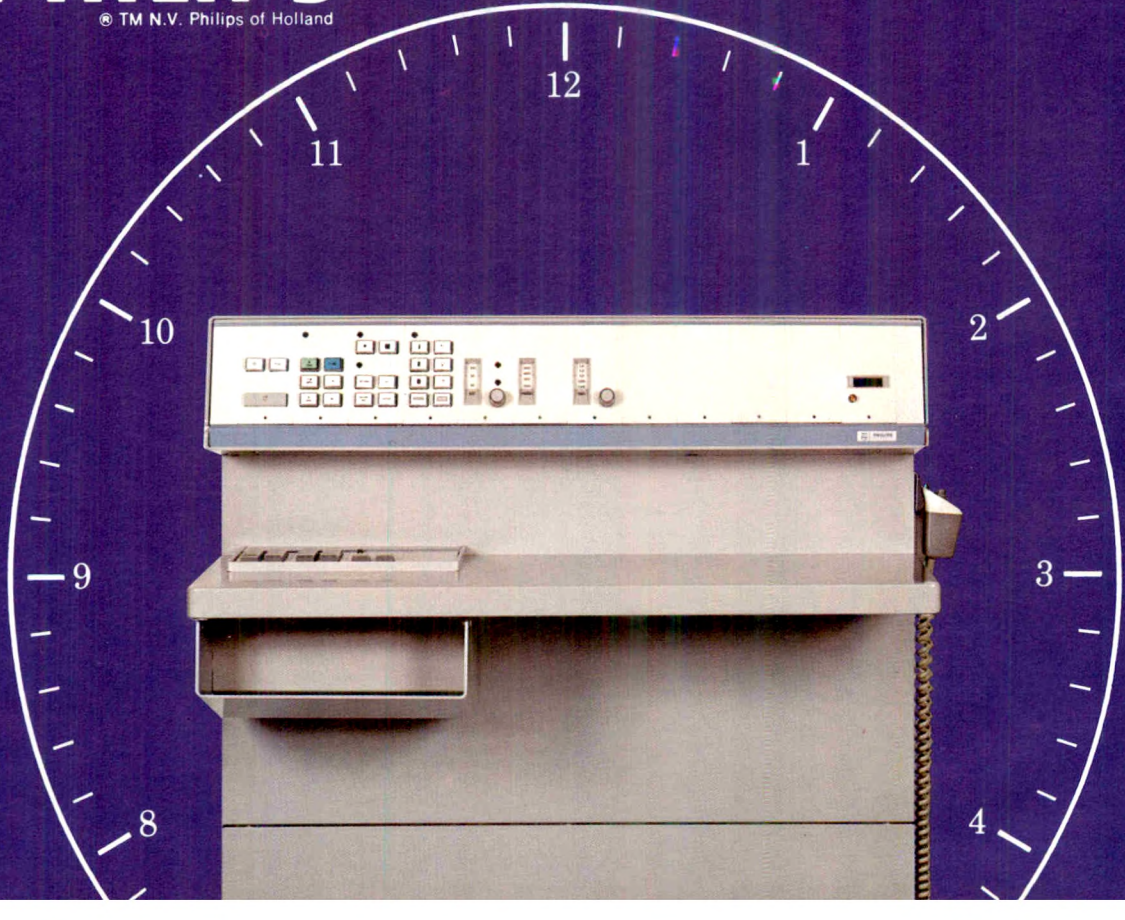

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CARDIAC CATHETERIZATION AND ANGIOCARDIOGRAPHY IN SEVERE NEONATAL HEART DISEASE *by* **Michael T. Gyepes**, *UCLA, Los Angeles, California, and* **William R. Vincent**, *Pennsylvania State Univ., University Park, Pennsylvania.* This monograph is written primarily for trainees in pediatric cardiology and pediatric cardiovascular radiology. Information is presented that has not been available in this form until now. The authors present a concise and logical approach to the diagnosis of severe congenital heart disease in the newborn. With the advent of open heart surgery in infancy and early childhood, the importance of neonatal diagnosis and management cannot be overemphasized. The information provided is to assist the trainee in sorting out the data before catheterization, as well as to help him ask the pertinent questions to be answered during the study. The book is organized around the acts of cardiac catheterization and angiocardiography and is divided into three parts. The first part covers the preliminary clinical and laboratory examination that must take place prior to catheterization. The authors present a broad functional classification of the lesions which most commonly cause symptoms in the first month of life. Their scheme of classification is based primarily on the x-ray appearance of the pulmonary vasculature (decreased, increased, or congested) and helps the trainee to focus on the questions of highest priority which need to be answered by the study. This section ends with a discussion of the indications and contraindications for emergency catheterization. The second part deals with the technical aspects of catheterization and angiocardiography, with particular emphasis on the special needs and problems of the unstable infant. This section is introduced by a discussion of equipment requirements. A different approach to catheterization of infants in each of the three functional groups is suggested. Part three deals with the question of what to do with the information that has been obtained. Throughout the chapters, the book is extensively illustrated. *'74, 184 pp., 317 il., $14.50*

MODERN THIN-SECTION TOMOGRAPHY *edited by* **Arnold Berrett**, *New York Medical College, New York;* **Sam Brunner**, *Gentofte Hospital, Copenhagen, Denmark; and* **Galdino E. Valvassori**, *Univ. of Illinois, Chicago. Foreword by* **Solve Welin**. *(21 Contributors)* This text, written by a number of prominent experts, clearly reflects the enormous advances diagnostic roentgenology has made in this special field, and indicates the important part it plays in otological diagnosis. The contributors provide chapters on the history of tomography and physical principles involved, as well as a description of much of the equipment available. These chapters are followed by discussion of tomographic anatomy, technical factors, and clinical applications of the method in various parts of the body. This diagnostic method appears to be most useful in the region of the head and neck, where the anatomical structures tend to be rather small and complex. Thus, a significant segment of the book is devoted to the clinical problems encountered in this region. *'73, 352 pp. (7 x 10) 496 il., 17 tables, $26.50*

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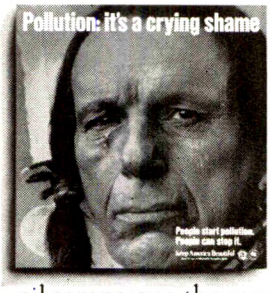

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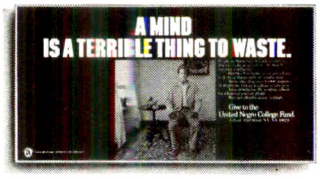

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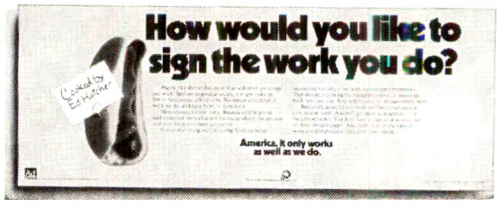

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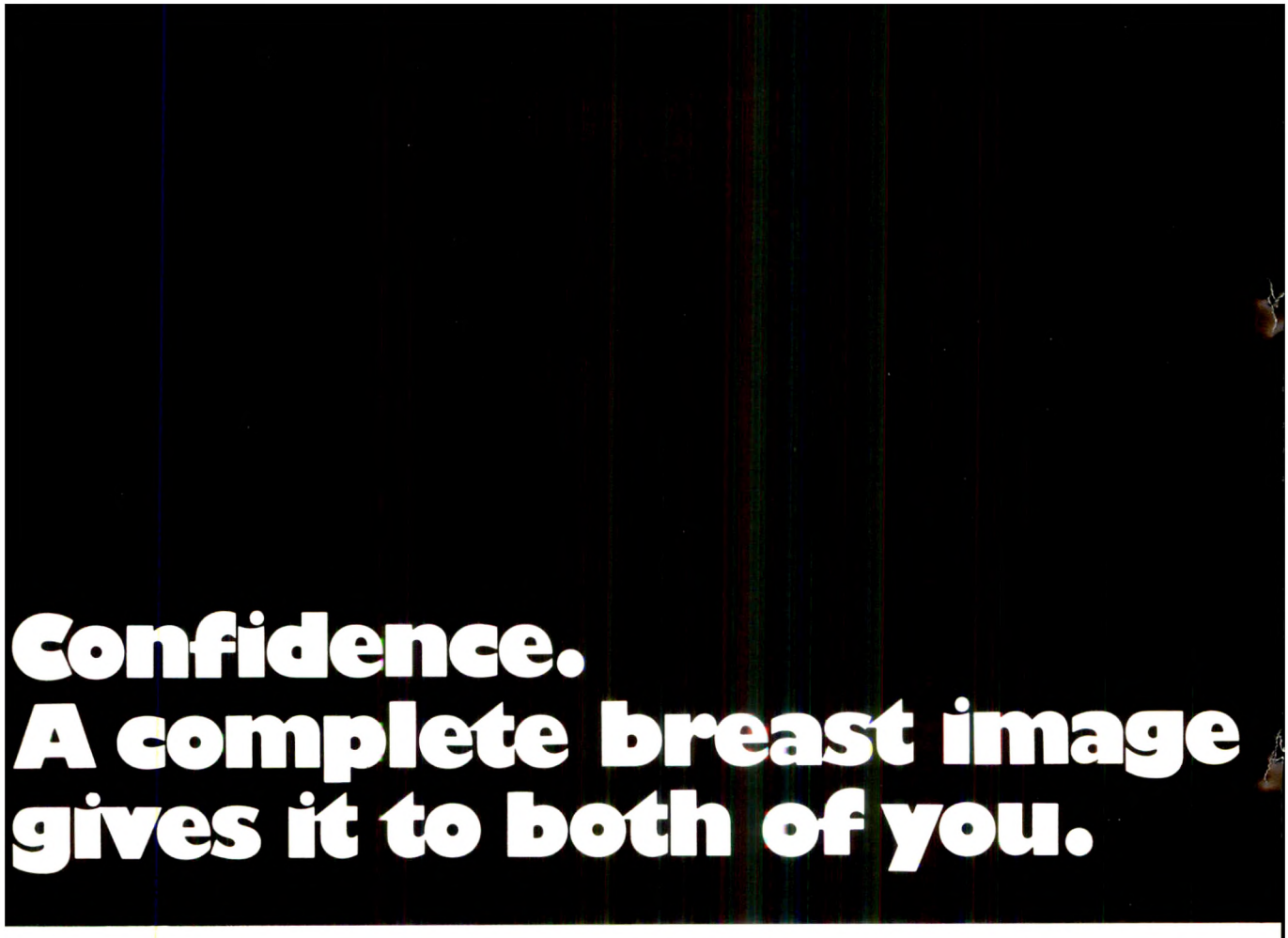

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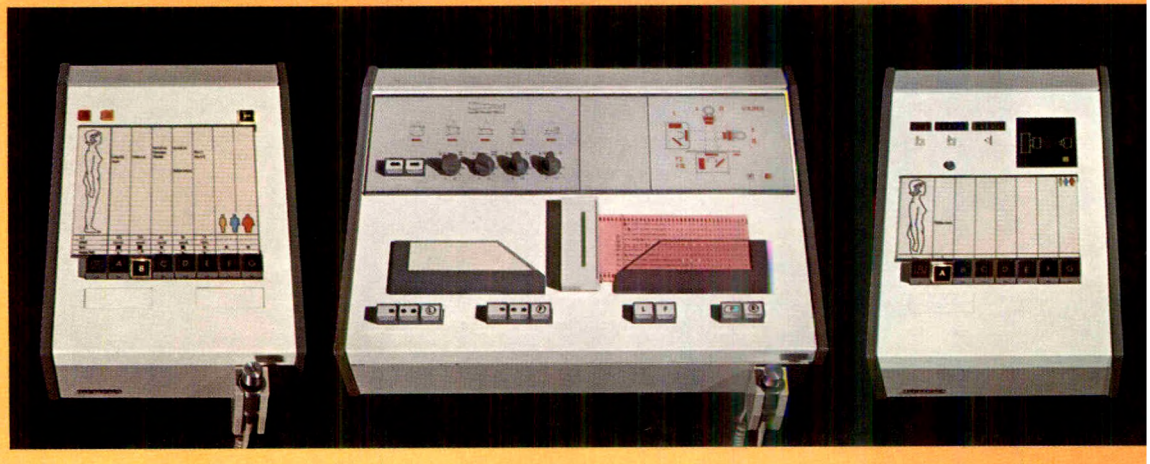

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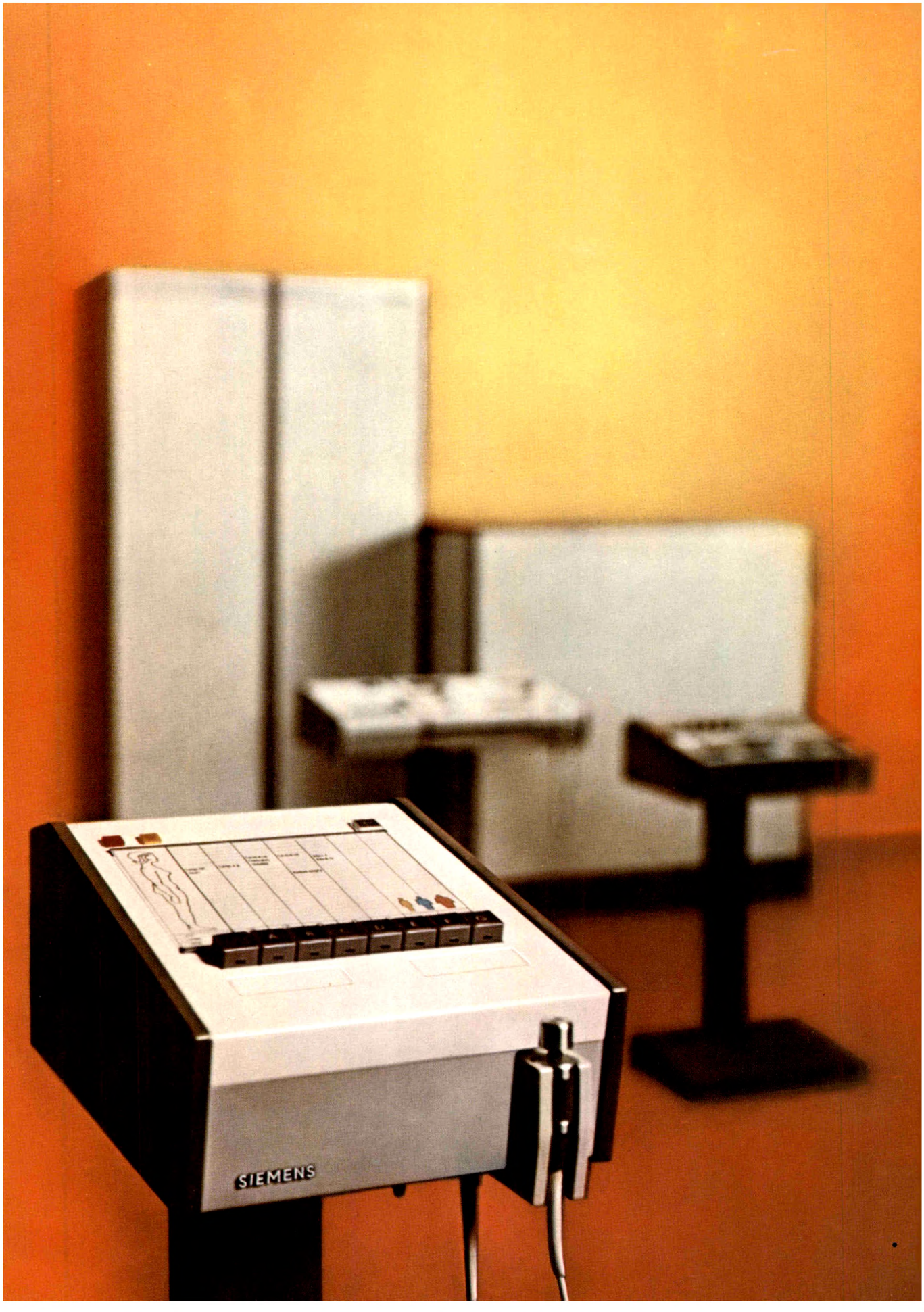
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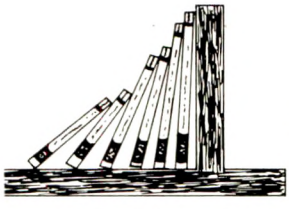

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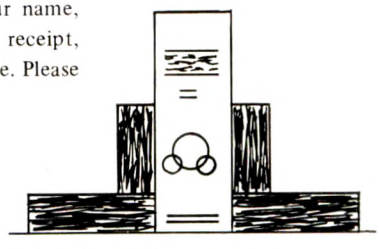

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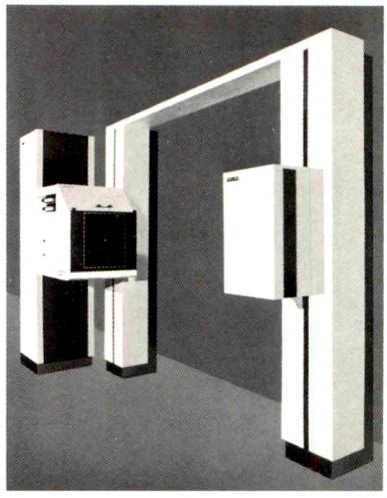

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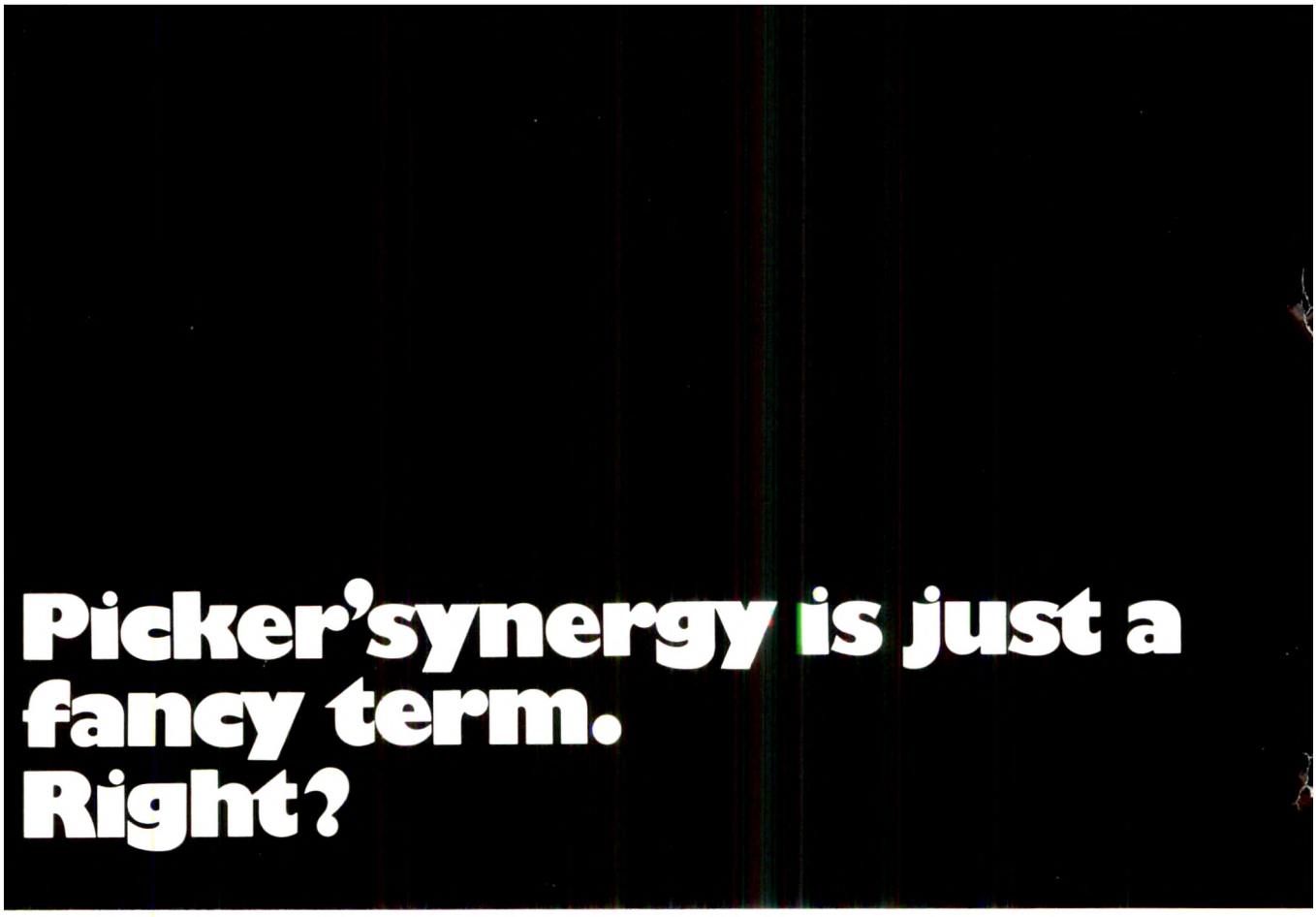

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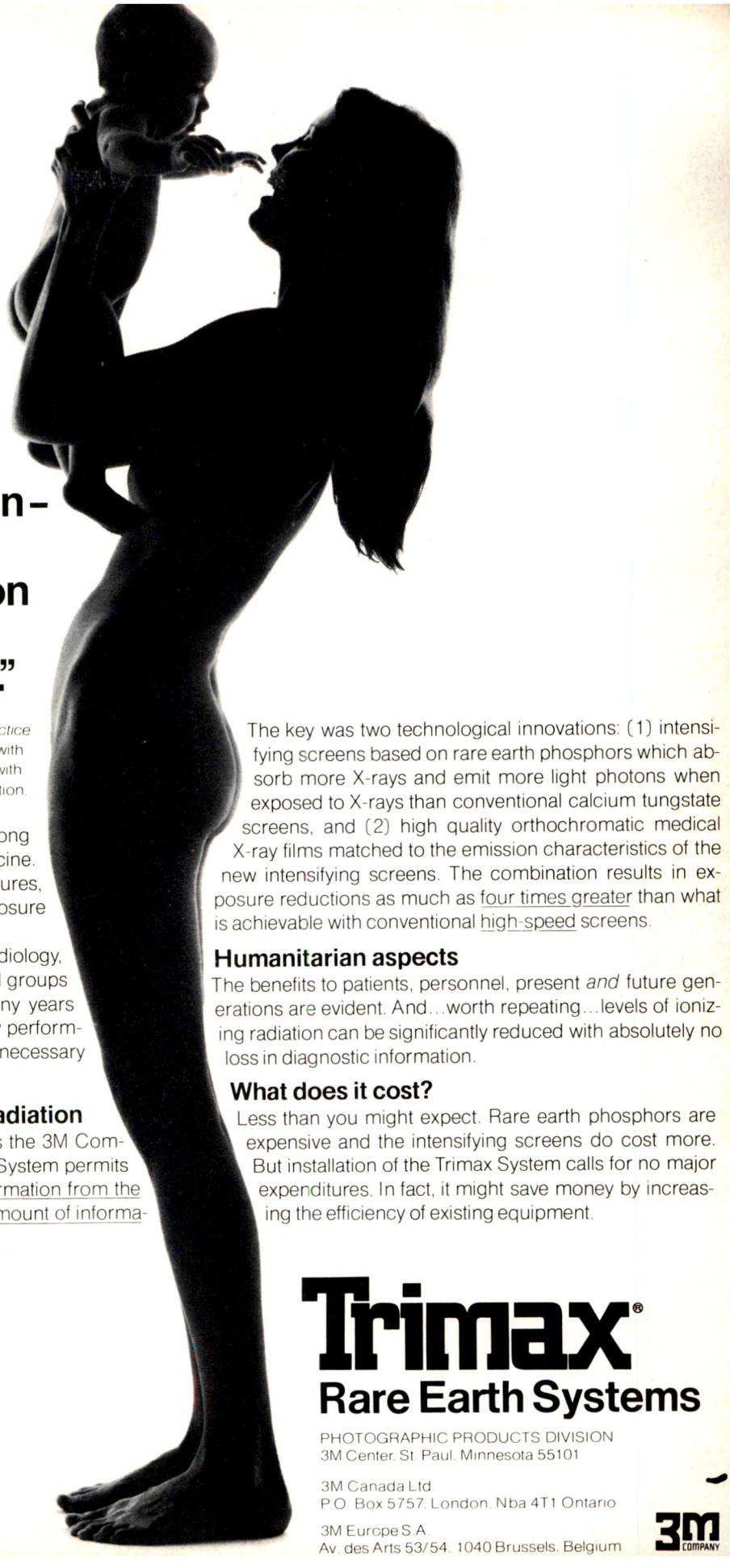

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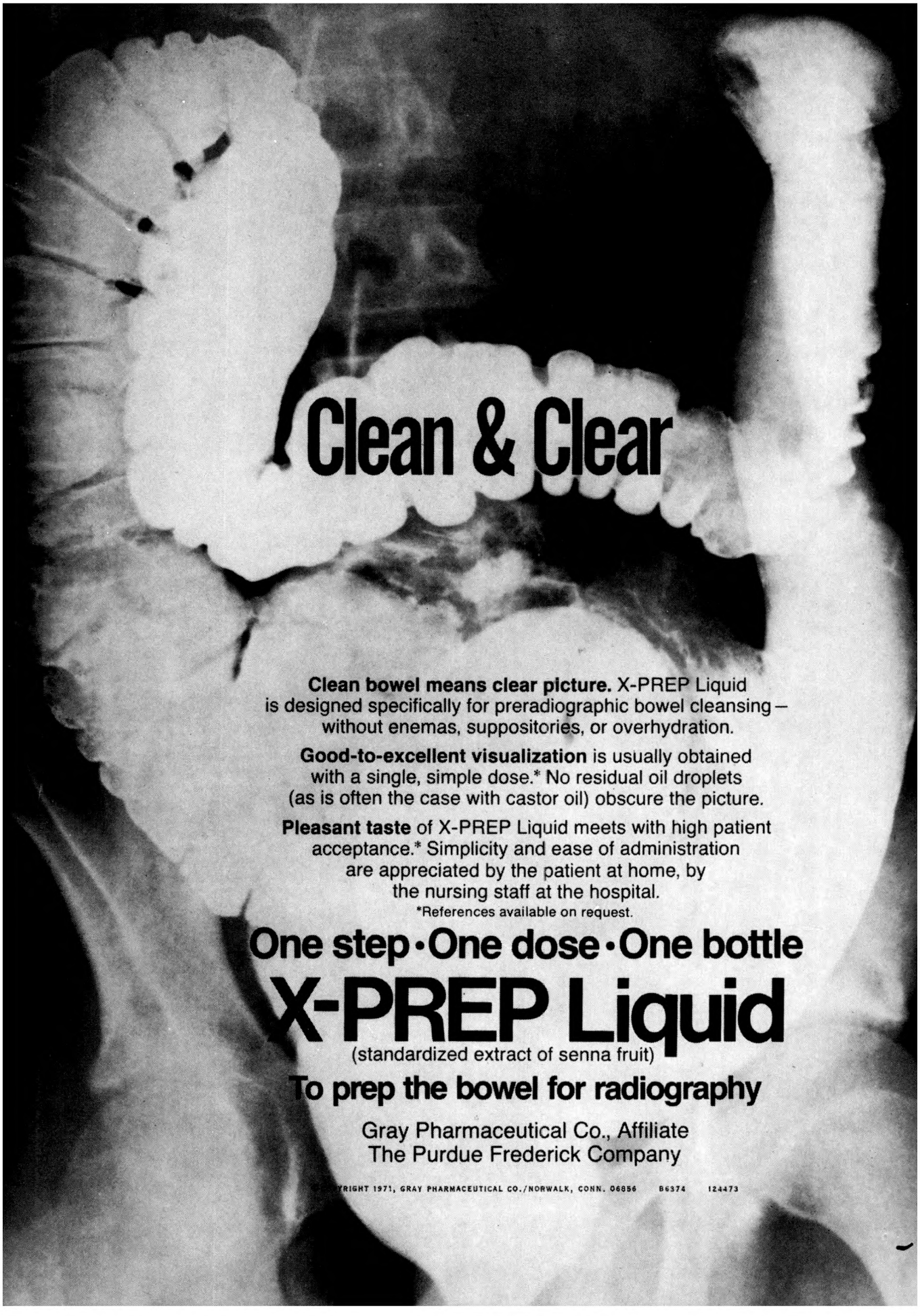

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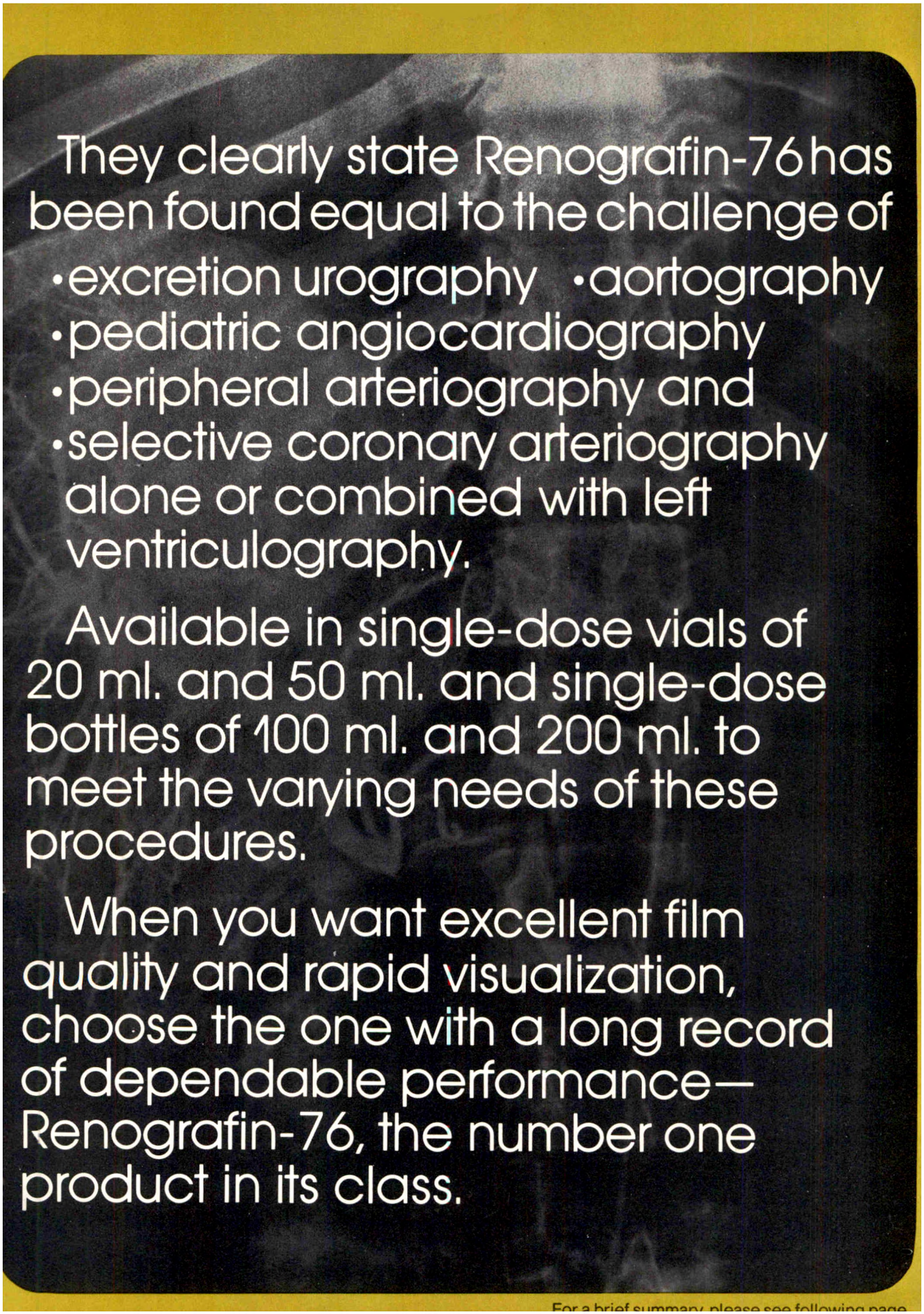
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CONTRAINDICATIONS: In patients with a hypersensitivity to salts of diatrizoic acid. Urography contraindicated in patients with anuria.

WARNINGS: A definite risk exists with the use of contrast agents in excretion urography in patients with multiple myeloma. There has been anuria with progressive uremia, renal failure and death. This risk of the procedure in these patients is not a contraindication; however, partial dehydration in preparation for study is not recommended since it may predispose for precipitation of myeloma protein in renal tubules. No therapy, including dialysis, has been successful in reversing this effect. Myeloma should be considered in persons over 40 before undertaking urographic procedures.

In cases of known or suspected pheochromocytoma, if the physician feels that the possible benefits outweigh the considered risks, radiopaque materials should be administered with extreme caution; however, an absolute minimum of material should be injected, the blood pressure should be assessed throughout the procedure, and measures for treating a hypertensive crisis should be available.

Contrast media may promote sickling in homozygous individuals when injected I.V. or intra-arterially. Although a history of sensitivity to iodine *per se* or to other contrast media is not an absolute contraindication, administration of diatrizoate requires extreme caution in such cases. Renografin-76 should be used in pregnant patients only when the physician deems its use essential to the welfare of the patient since safe use during pregnancy has not been established. Perform thyroid function tests prior to administration of Renografin-76 since iodine-containing contrast agents may alter the test results.

Weigh the inherent risks against necessity for performing *angiocardiography* in cyanotic infants and patients with chronic pulmonary emphysema. In *pediatric angiocardiography*, a dose of 10 to 20 ml. may be particularly hazardous in infants weighing less than 7 kg.; this risk is probably significantly increased if these infants have preexisting right heart "strain," right heart failure, and effectively decreased or obliterated pulmonary vascular beds. Perform *urography* with extreme caution in persons with severe concomitant hepatic and renal disease. Perform *selective coronary arteriography* only in selected patients and those in whom expected benefits outweigh the procedural risk.

PRECAUTIONS: Diagnostic procedures involving use of contrast agents should be performed under the direction of personnel with prerequisite training and a thorough knowledge of the particular procedure. Appropriate facilities should be available for coping with situations which may arise as a result of the procedure and for emergency treatment of severe reactions to the contrast agent itself; competent personnel and emergency facilities should be available for at least 30 to 60 minutes after I.V. administration since delayed reactions have been known to occur. These severe life-threatening reactions suggest hypersensitivity to the contrast agent. A personal or family history of asthma or allergy or a history of a previous reaction to a contrast agent warrants special attention and may predict more accurately than pretesting the likelihood of a reaction although not the type nor severity of the reaction in the individual. The value of any pretest is questionable. The pretest most performed is the slow I.V. injection of 0.5 to 1.0 ml. of the preparation prior to injection of the full dose; however, the absence of a reaction to the test dose does not preclude the possibility of reaction to the full diagnostic dose. Should the test dose produce an untoward response, the necessity for continuing the examination should be re-evaluated. If deemed essential, examination should proceed with all possible caution. In rare instances, reaction to the test dose may be extremely severe; therefore, close observation and facilities for emergency treatment are indicated.

Renal toxicity has been reported in a few patients with liver dysfunction who were given oral cholecystographic agents followed by urographic agents; therefore, if known or suspected hepatic or biliary disorder exists, administration of Renografin-76 should be postponed following the ingestion of cholecystographic agents. Consider the functional ability of the kidneys before injecting Renografin-76. Use cautiously in severely debilitated patients and in those with marked hypertension. Bear in mind the possibility of thrombosis when using percutaneous techniques.

In *excretion urography*, adequate visualization may be difficult or impossible in uremic patients or others with severely impaired renal function (see Contraindications). In *aortography* repeated intra-aortic injections may be hazardous; this also applies to *pediatric angiocardiography* particularly in infants weighing less than 7 kg. (see Warnings). In *peripheral arteriography*, hypotension or moderate decreases in blood pressure seem to occur frequently with intra-arterial (brachial) injections; this is transient and usually requires no treatment. Monitor blood pressure during the immediate 10 minutes after injection. It is recommended that *selective coronary arteriography* not be performed for about 4 weeks after diagnosis of myocardial infarction; mandatory prerequisites to this procedure are experienced personnel, ECG monitoring apparatus, and adequate facilities for immediate resuscitation and cardioversion.

ADVERSE REACTIONS: Nausea, vomiting, flushing, or a generalized feeling of warmth are the reactions seen most frequently with intravascular injection. Symptoms which may occur are chills, fever, sweating, headache, dizziness, pallor, weakness, severe retching and choking, wheezing, a rise or fall in blood pressure, facial or conjunctival petechiae, urticaria, pruritus, rash, and other eruptions, edema, cramps, tremors, itching, sneezing, lacrimation, etc. Antihistaminic agents may be of benefit; rarely, such reactions may be severe enough to require discontinuation of dosage. There have been a few reports of a burning or stinging sensation or numbness, of venospasm or venous pain, and of partial collapse of the injected vein. Neutropenia or thrombophlebitis may occur. Severe reactions which may require emergency measures (see Precautions) are a possibility and include cardiovascular reaction characterized by peripheral vasodilatation with hypotension and reflex tachycardia, dyspnea, agitation, confusion, and cyanosis progressing to unconsciousness. An allergic-like reaction ranging from rhinitis or angioneurotic edema to laryngeal or bronchial spasm or anaphylactoid shock may occur. Temporary renal shutdown or other nephropathy may occur.

Adverse reactions as a consequence of *excretion urography* include cardiac arrest, ventricular fibrillation, anaphylaxis with severe asthmatic reaction, and flushing due to generalized vasodilatation. Risks of *aortography* procedures include injury to aorta and neighboring organs, pleural puncture, renal damage (including infarction and acute tubular necrosis with oliguria and anuria), accidental selective filling of right renal artery during translumbar procedure in presence of preexistent renal disease, retroperitoneal hemorrhage from translumbar approach, spinal cord injury and pathology associated with syndrome of transverse myelitis, generalized petechiae, and death following hypotension, arrhythmia, and anaphylactoid reactions. In *pediatric angiocardiography*, arrhythmia and death have occurred. During *peripheral arteriography*, hemorrhage from puncture site, thrombosis of the vessel, and brachial plexus palsy (following axillary artery injection) have occurred. During *selective coronary arteriography* and *selective coronary arteriography with left ventriculography*, transient ECG changes (most patients); transient arrhythmias (infrequent); ventricular fibrillation (from manipulation of catheter or administration of medium); hypotension; chest pain; myocardial infarction; transient elevation of creatinine phosphokinase (occurred in about 30% of patients tested); fatalities have been reported; hemorrhage, thrombosis, pseudoaneurysms at puncture site, dislodgment of arteriosclerotic plaques, dissection of coronary vessels, and transient sinus arrest have occurred due to the procedure.

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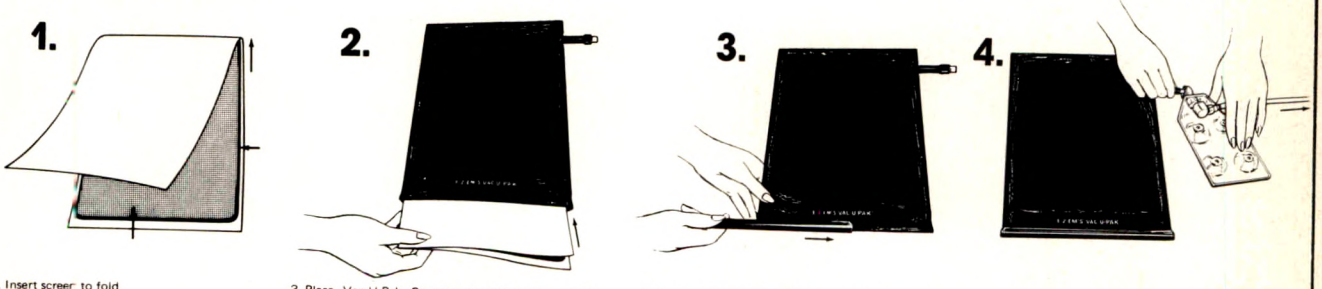

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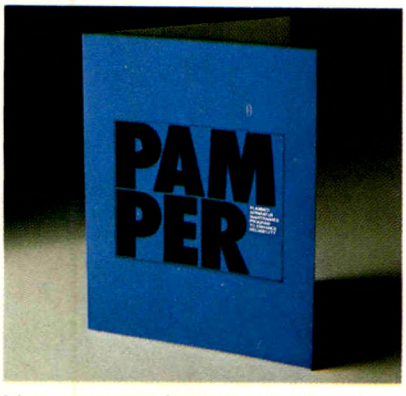

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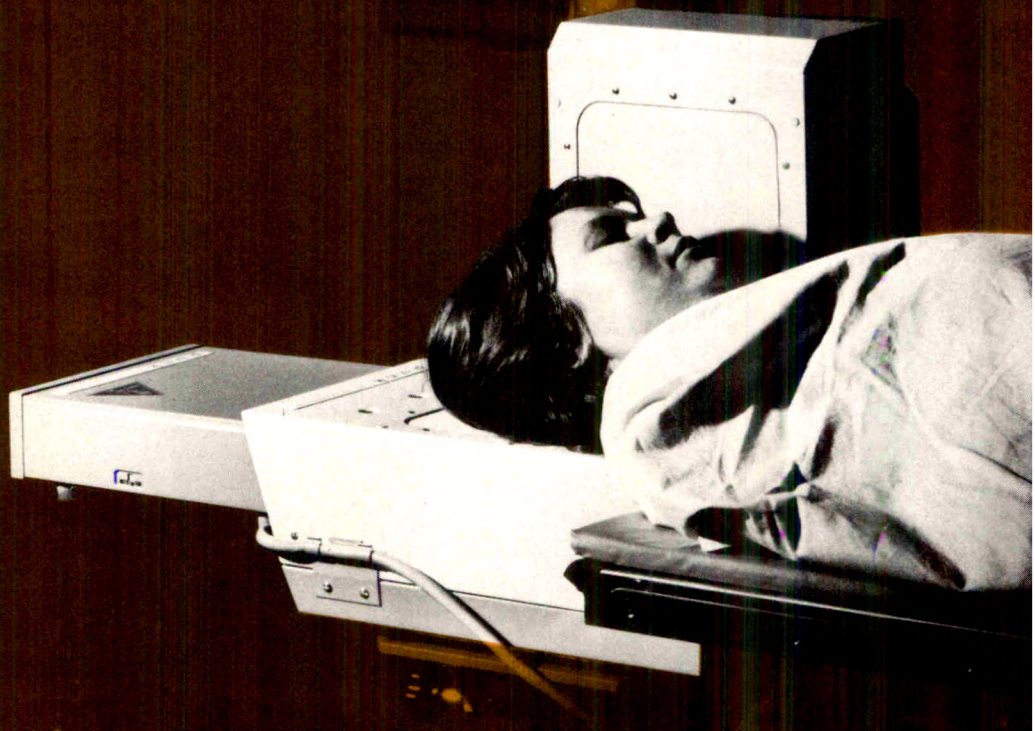

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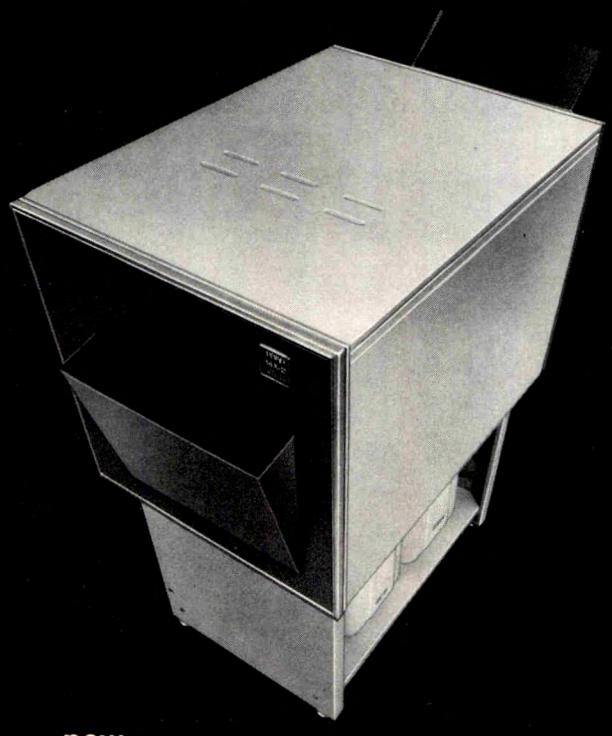

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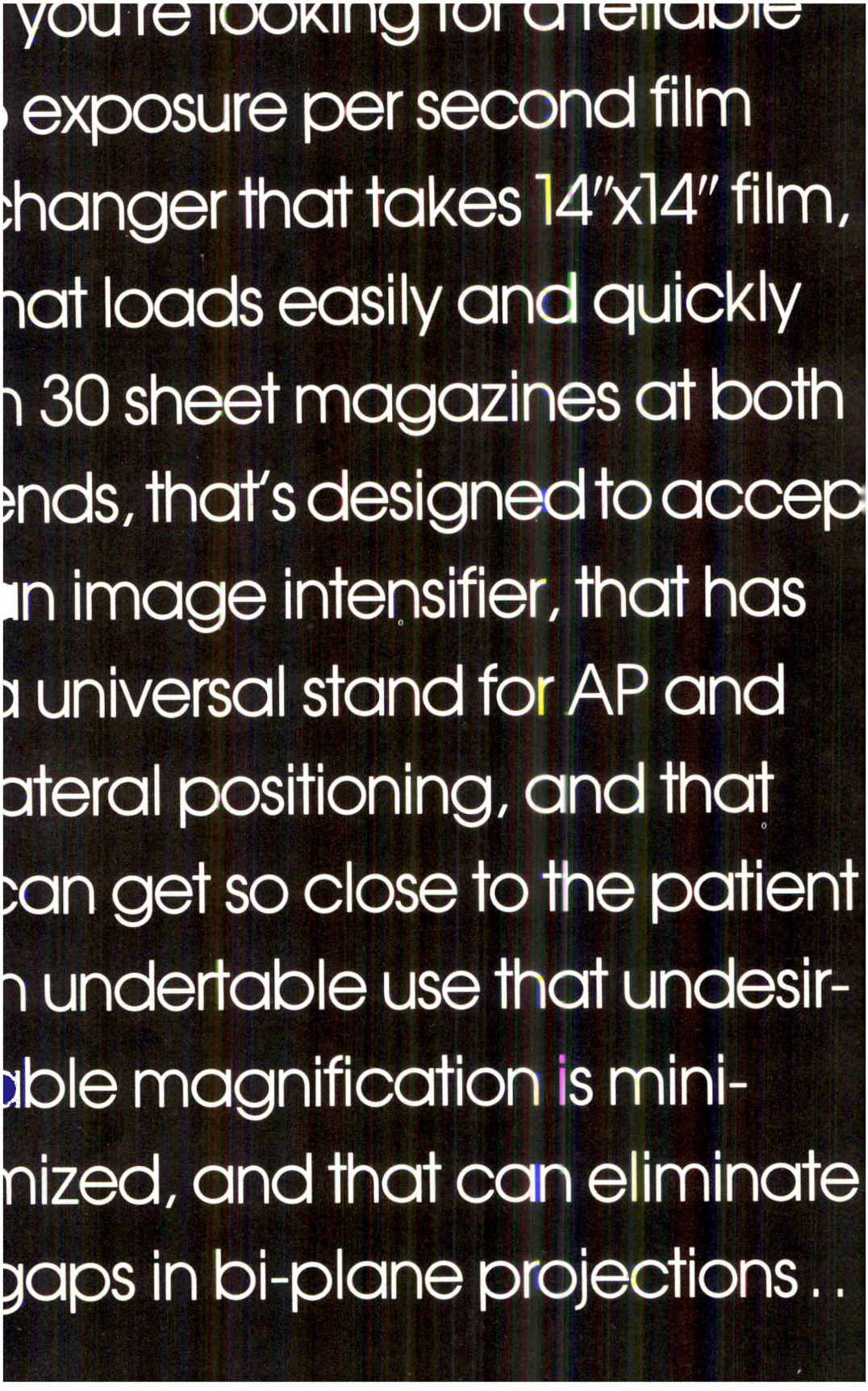
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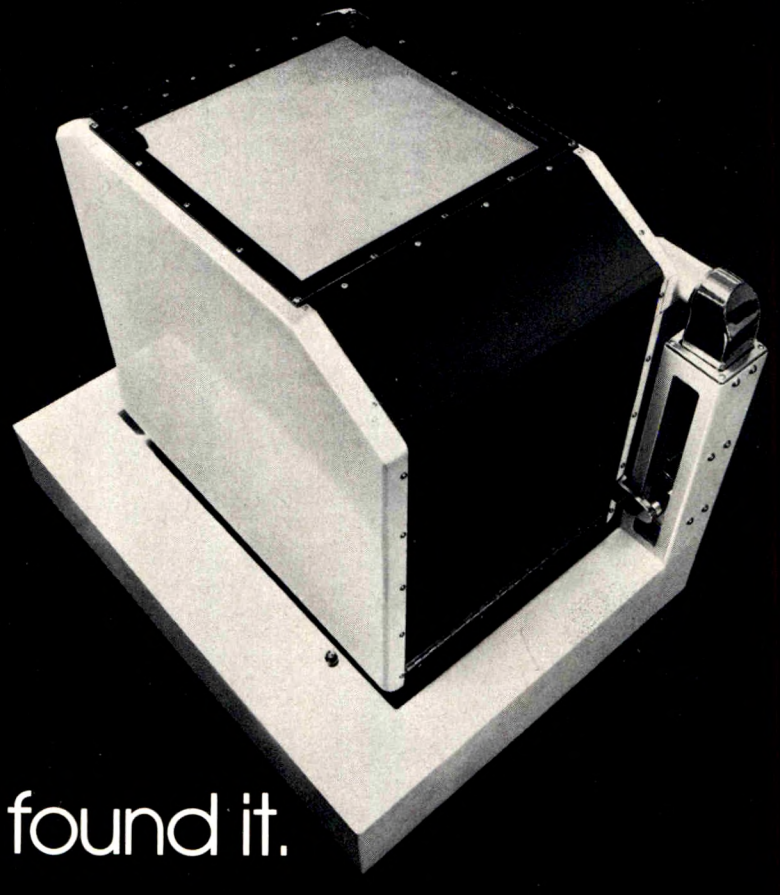

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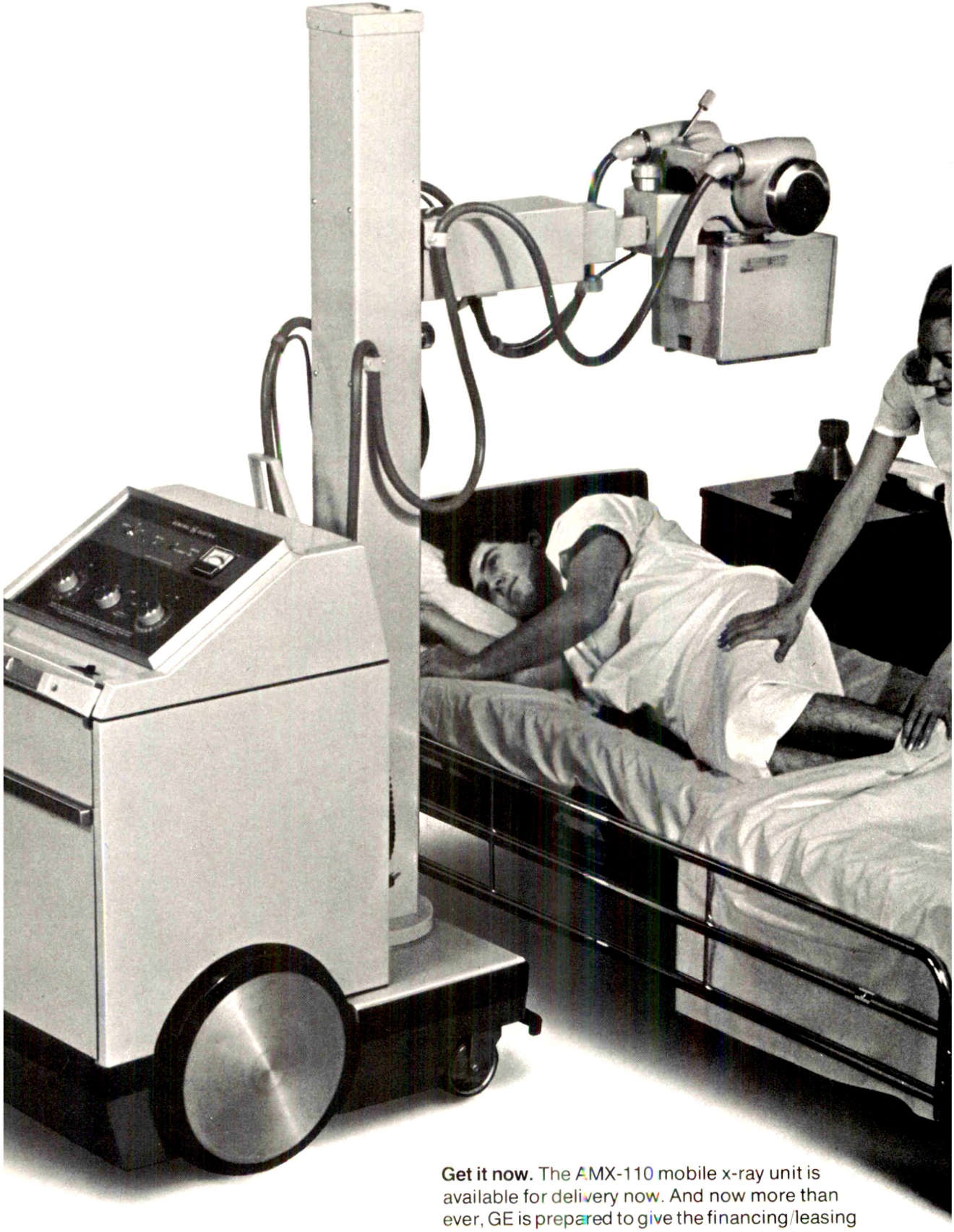

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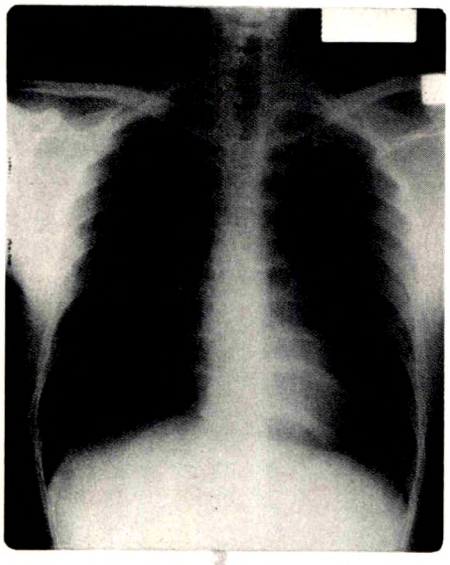

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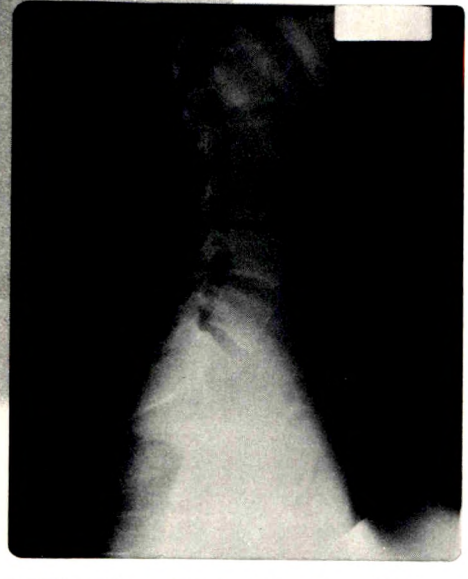

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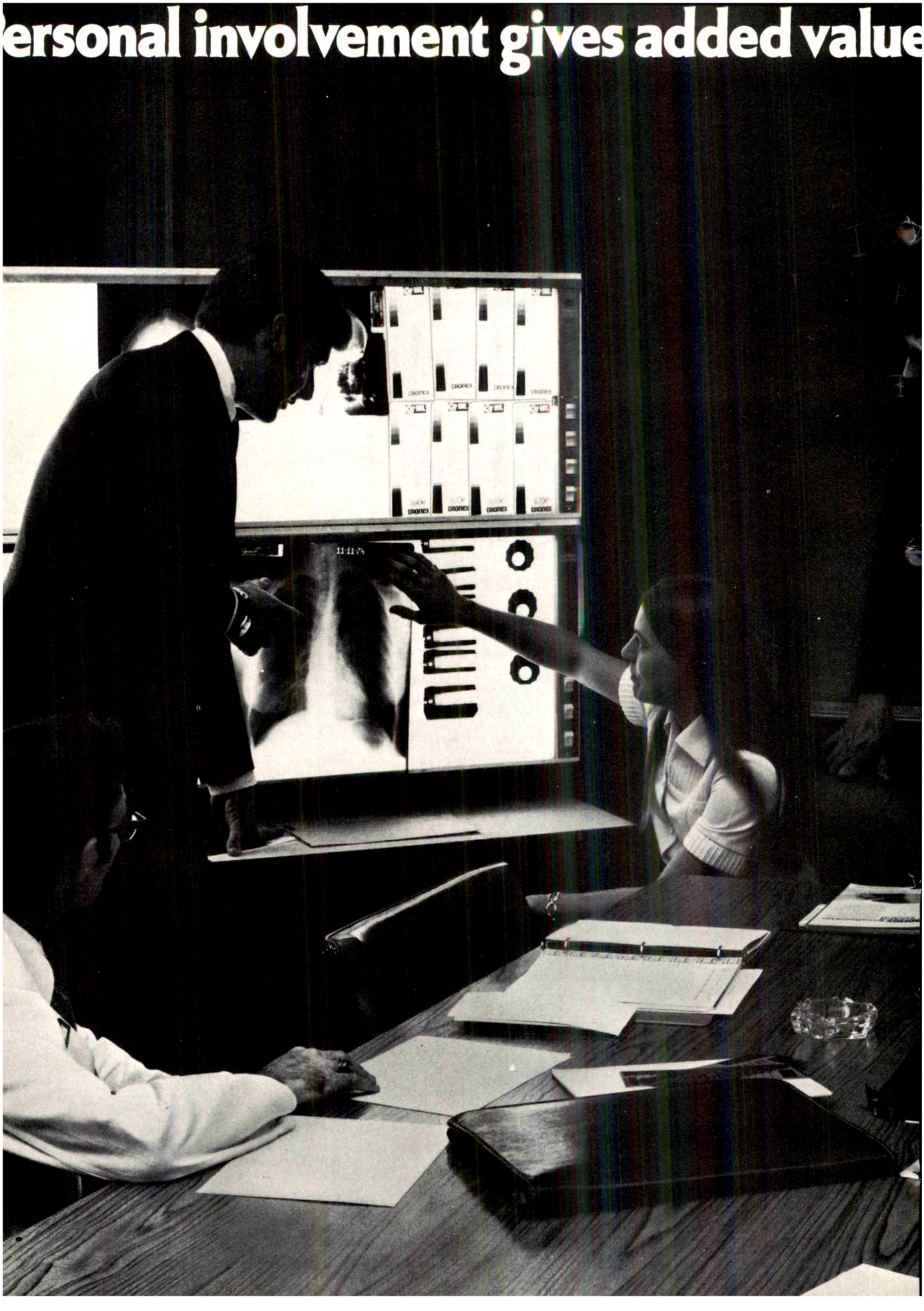

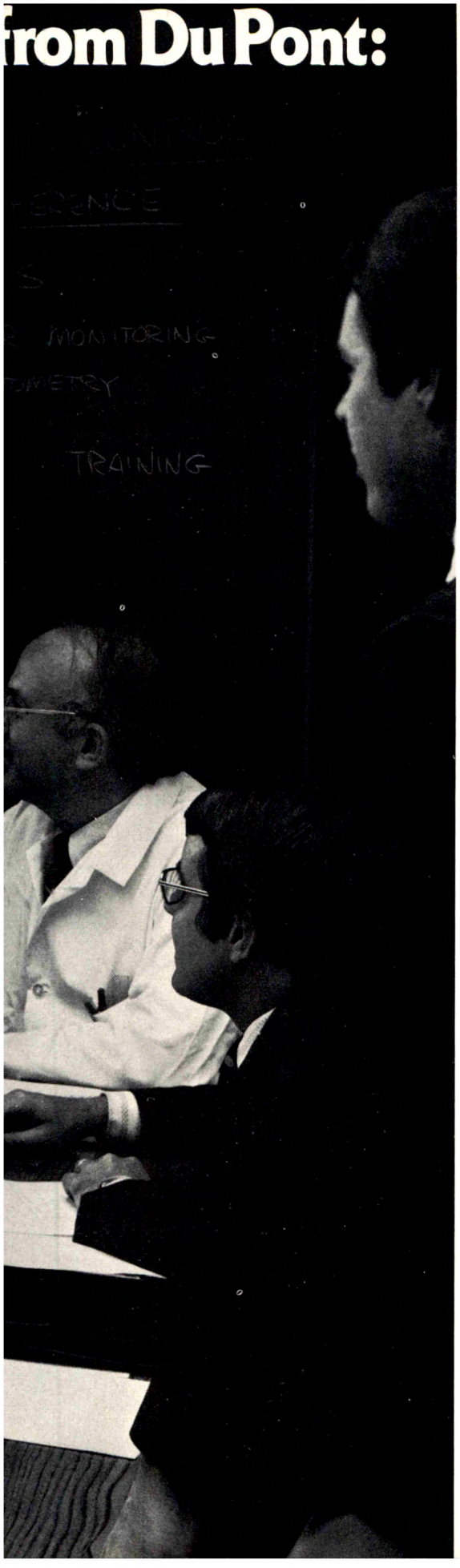

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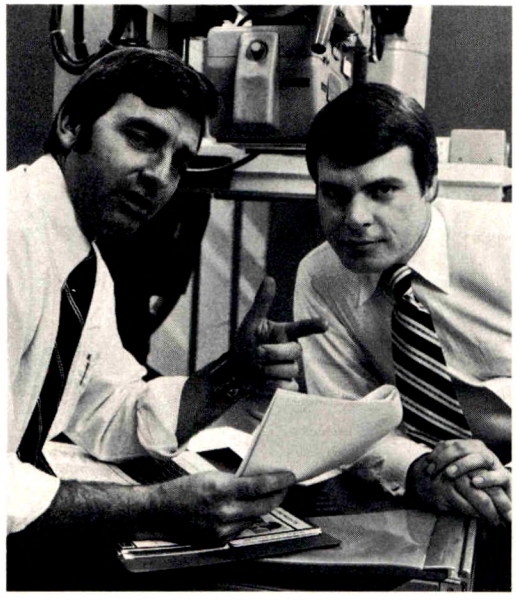

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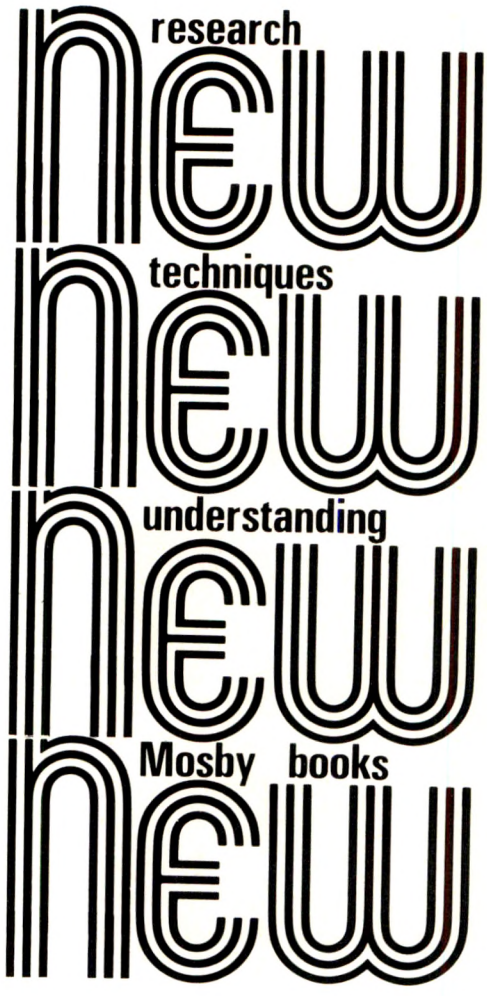

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XERORADIOGRAPHY

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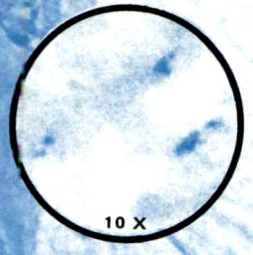

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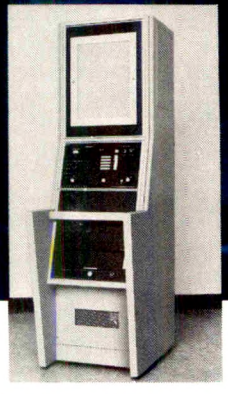

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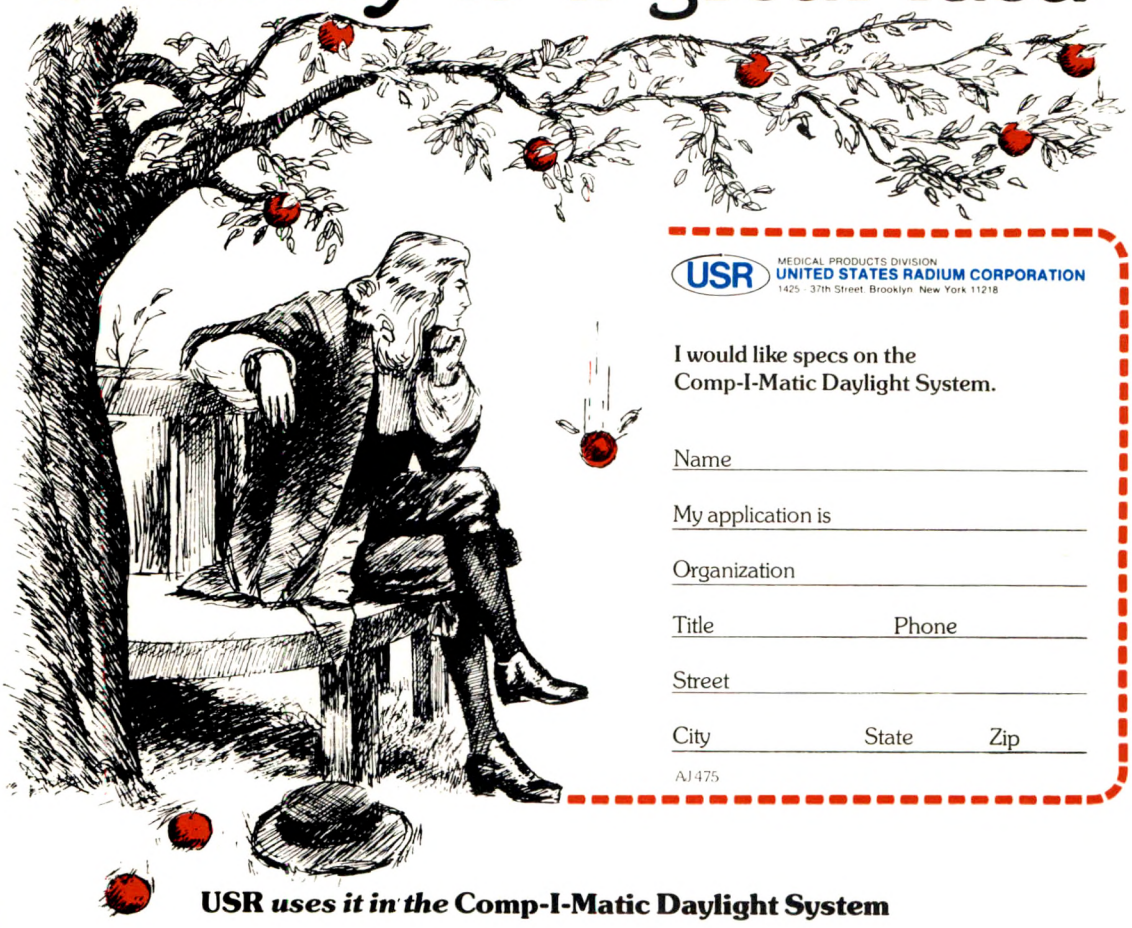

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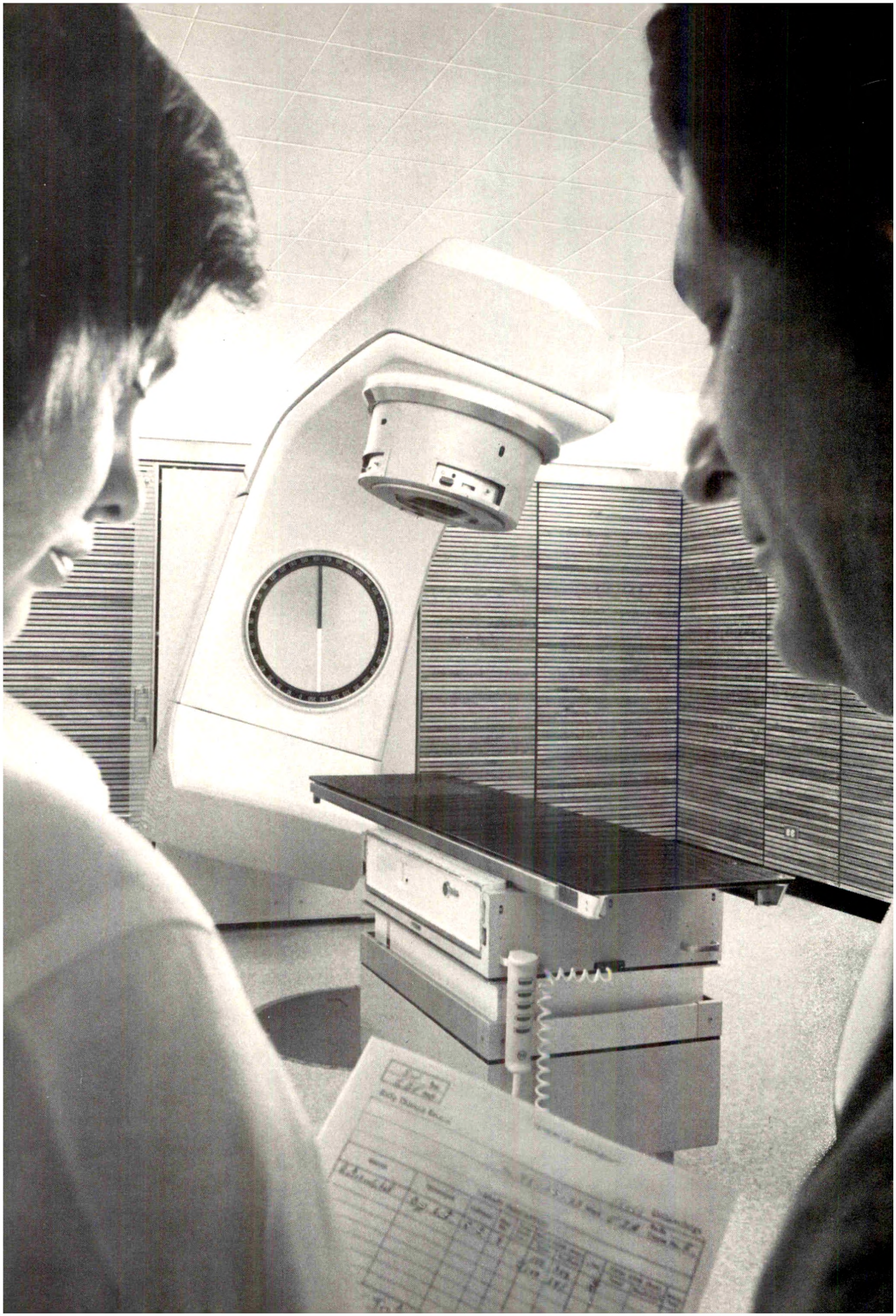

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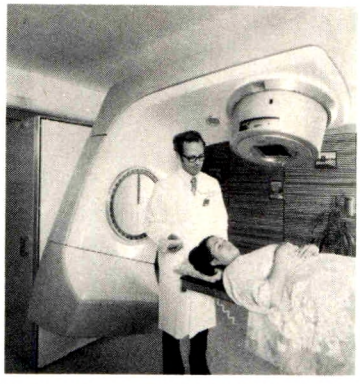

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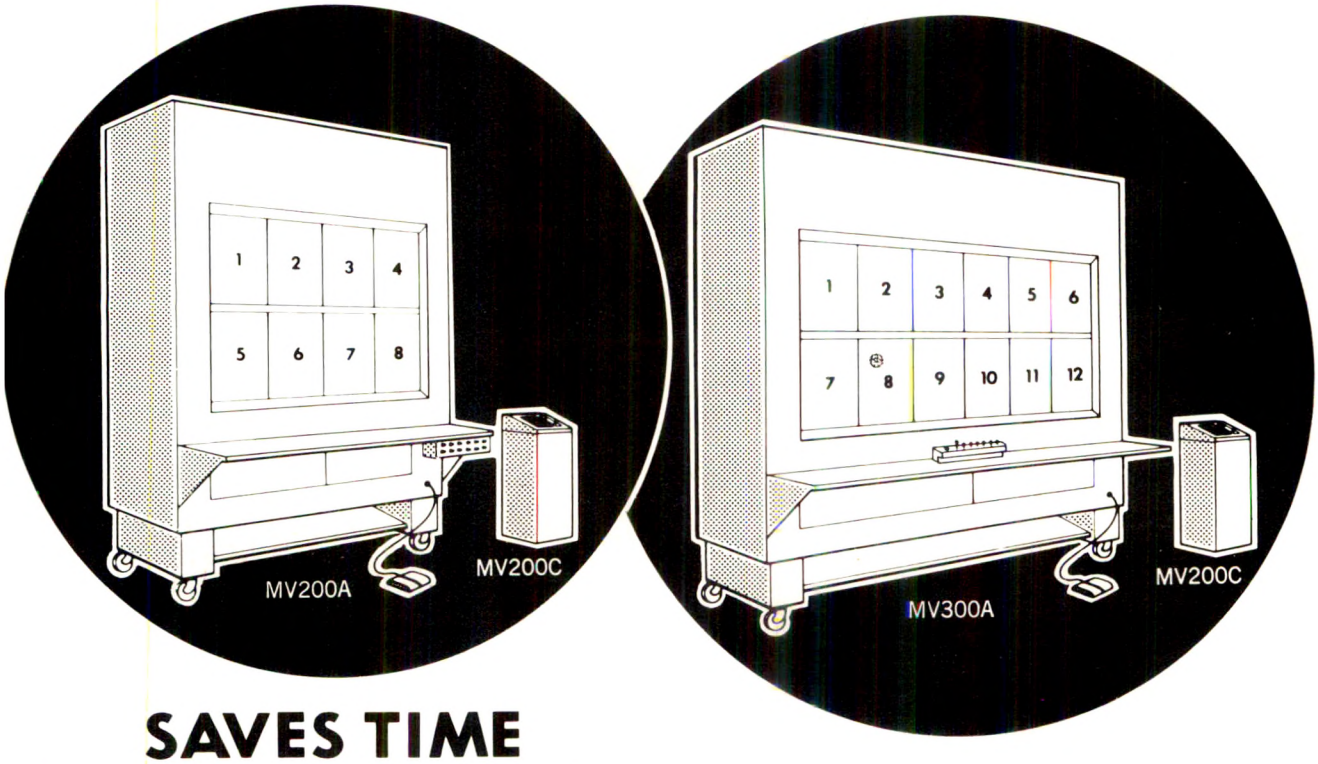

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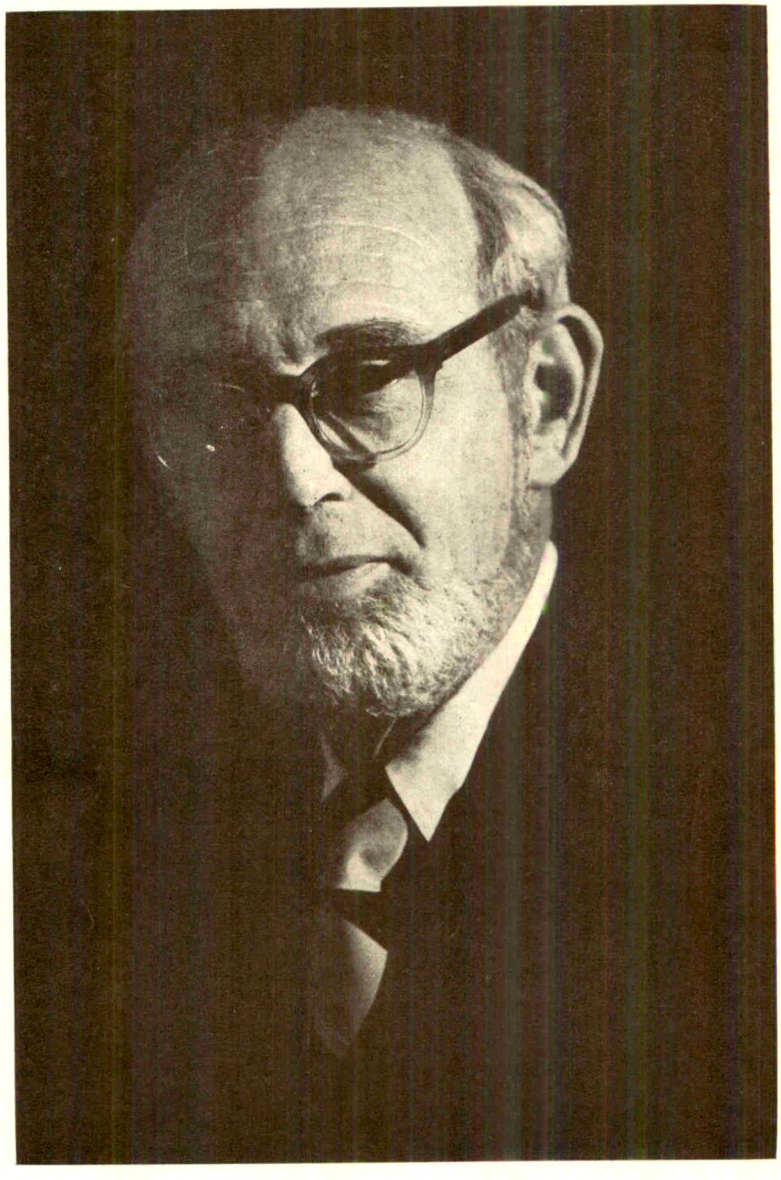

BENJAMIN H. LANDING, M.D.
NEUHAUSER LECTURER, 1974

THE AMERICAN JOURNAL OF ROENTGENOLOGY
RADIUM THERAPY AND NUCLEAR MEDICINE

VOL. 123 APRIL, 1975 No. 4

SYNDROMES OF CONGENITAL HEART DISEASE WITH TRACHEOBRONCHIAL ANOMALIES*

EDWARD B. D. NEUHAUSER LECTURE, 1974

By BENJAMIN H. LANDING, M.D.

AT least 10 syndromes in which a tracheobronchial anomaly coexists with a congenital heart malformation have been described. In several of these, radiologic demonstration of abnormal tracheal air-column, of abnormal bronchial branching pattern, of other radiologically demonstrable tracheal or bronchial malformation, or of combinations of these, with or without demonstration of relevant abnormalities of the gastrointestinal tract, of visceral situs, of the skeleton or of the urinary tract, can be of value in predicting the presence of, or in indicating the type of, congenital heart disease. On the other hand, for some of the syndromes of association of congenital heart disease with tracheobronchial anomaly, clinical recognition of the cardiac lesion will usually precede, and be a clue facilitating demonstration of, significant malformation of the respiratory tract.

This Lecture summarizes the better known of these syndromes, on the basis of patient material in the files of the Department of Pathology, and of the Cardiac Registry, of the Childrens Hospital of Los Angeles, with emphasis on the significance of radiologically demonstrable anomalies of the tracheobronchial tree for the diagnosis, or confirmation of diagnosis, of specific malformation syndromes which also include congenital cardiac malformation. For several of these syndromes, which are specific genetic diseases, precise diagnosis permits accurate genetic counseling, and for others, their accurate identification furnishes strong indication of the nature and extent of appropriate surgical or other therapy.

SYNDROMES OF CONGENITAL HEART DISEASE WITH TRACHEOESOPHAGEAL FISTULA

(THE VATER, VACTEL, ARTICLE AND POSSIBLY OTHER COMPLEXES)

Recent medical literature suggests that there are at least 2 complexes or constellations of congenital malformations associated with esophageal atresia and tracheo-

* Presented as the Edward B. D. Neuhauser Annual Lecture, at the Seventeenth Annual Meeting of the Society for Pediatric Radiology, San Francisco, California, September 23, 1974.

From the Departments of Pathology and Pediatrics, Childrens Hospital of Los Angeles and University of Southern California School of Medicine, Los Angeles, California.

esophageal fistula.[4,5] The acronyms VATER and VACTEL list the components of each complex—for the former, vertebral, anal, tracheoesophageal, and radial, renal, or both (VATER), anomalies, and for the latter, vertebral, anal, cardiac, tracheoesophageal, and limb (VACTEL) malformations. Both complexes, as described, need not produce all the indicated features in all patients, so that each may be, in a sense, a segment abstracted from a spectrum of anomaly associations. If this is so, the predictive power of the demonstration of one or more of the components of either complex, in a patient, for the other features of the complex, will be relatively low, whereas the predictive power of such demonstration will obviously be greater for malformations which tend to occur together with frequency significantly greater than that expected by chance.

In order to establish which of these appears to be the case, we have reviewed all patients, autopsied from 1961–1973 inclusive at the Childrens Hospital of Los Angeles who had esophageal atresia with tracheoesophageal fistula (EA-TEF), with other congenital malformations. As Table I illustrates, the frequency of various other anomalies in patients with EA-TEF differs, depending on whether the study population consists of all such patients who have any other anomaly, of such patients who have 3 or more other anomalies, or of those who have 1 or more of cardiac, renal, anal or limb anomalies (those anomalies found in the VATER and VACTEL complexes in addition to EA-TEF, except for vertebral anomalies, omitted because of the apparently low frequency and possibly incomplete ascertainment at autopsy). To attempt to ascertain the utility of the VATER and VACTEL concepts, then, from our material, one must decide whether anal, renal, cardiac or limb anomalies occur in association with each other with greater than expected frequency in patients with EA-TEF. Figures 1–3 compare the expected with the observed coincidence frequencies of these anomalies in the 3 populations of patients with EA-TEF chosen for illustration. For population 1, 28 infants with EA-TEF plus any other anomaly, the data support the validity of the VATER complex, since renal, anal and extremity anomalies do appear to associate together. How-

Table I

INCIDENCE OF MALFORMATIONS IN THREE GROUPS OF PATIENTS WITH ESOPHAGEAL ATRESIA AND TRACHEOESOPHAGEAL FISTULA

	EA-TEF, other anomaly		EA-TEF, one or more of cardiac, renal, anal, limb anomalies		EA-TEF, three or more other anomalies	
	No.	Per cent	No.	Per cent	No.	Per cent
Total in group	28		22		11	
Intestine, other	13	46	10	45	4	36
Cardiac	11	39	11	50	5	46
Renal/urinary tract	11	39	11	50	7	64
Limb	10	36	10	45	7	64
Anal	7	25	7	32	7	64
Accessory spleen	6	21				
Duodenal atresia, annular pancreas	6	21	5	23	3	27
Down syndrome	4	14				
Vertebral anomalies	4	14				
Biliary tract, other	4	14				
Central nervous system	3	11			1	9
Etc.	8	28				29

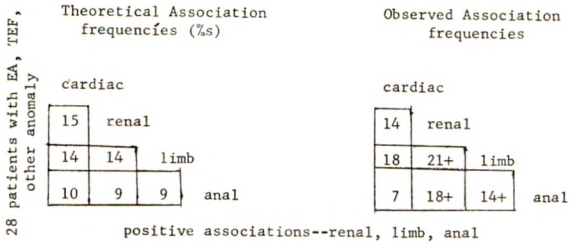

Fig. 1. Population 1.

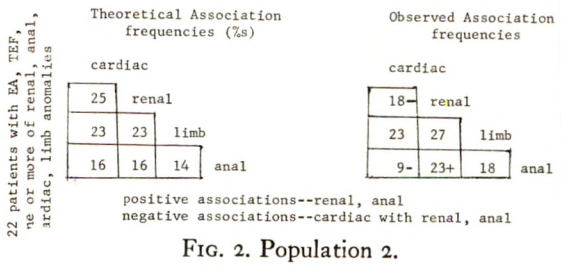

Fig. 2. Population 2.

TREND OF ASSOCIATIONS

Populations	1	2	3
Cardiac × renal	R	−	R
Cardiac × limb	R	R	R
Cardiac × anal	R	−	+
Renal × limb	+	R	R
Renal × anal	+	+	R
Limb × anal	+	R	R

R = frequency of association appears random; + = frequency of association appears greater than random; − = frequency of association appears less than random.

ever, for population 2, 22 infants with EA-TEF plus one or more of renal, anal, cardiac and limb anomalies, the support of the VATER complex is weaker, and population 3, 11 infants with 3 or more anomalies in addition to EA-TEF, if anything provides weak support for the validity of the VACTEL rather than the VATER complex. From the data of Table 1, which indicate that the probability of the presence of major duodenal anomaly (duodenal atresia or annular pancreas) or of other intestinal anomaly (chiefly malrotation) in infants with EA-TEF is under-represented by the VATER and VACTEL concepts, and from the analyses given in Figures 1–3 which show that none of cardiac, renal, anal and limb anomalies are significantly positively associated with each other in all 3 subsets of infants with EA-TEF studied, one can reasonably propose that the VATER and VACTEL patterns result from chance association of the appropriate anomalies in patients with EA-TEF who come from a population that has greater than 20 per cent chance of having, in addition to EA-TEF, each of renal, anal, cardiac, limb, duodenal and other intestinal anomalies. The nearest acronym we can suggest to indicate what may be the true situation, the spectrum of other anomalies most associated with EA-TEF, is the ARTICLE complex (anal, renal, tracheoesophageal, intestinal, cardiac, limb). (Alternatives might be TREACLE, for tracheal, renal, esophageal, anal, cardiac, limb, etc., or LEATHER, for limb, esophagus, anus, trachea, heart, etc., and renal).

The cardiac anomalies in the patients with esophageal atresia and tracheoesophageal fistula included in Table 1 are listed in Table 11. As can be seen, the most frequent are ventricular septal defect (8 patients—73 per cent of patients with a cardiac malformation), atrial septal defects (5 patients—45 per cent of those with congenital heart disease), and conotruncal anomalies (4 patients—36 per cent). The series may not be large enough for certainty, but it is of interest that the relatively common conditions, transposition of the great arteries, hypoplastic left heart complex and patent ductus arteriosus, did not occur in this group of patients with EA-TEF.

ASPLENIA (IVEMARK SYNDROME)

This malformation complex has been,

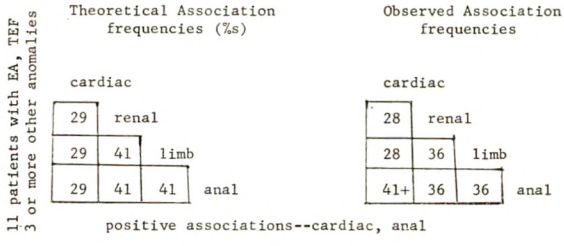

Fig. 3. Population 3.

Table II

CARDIOVASCULAR ANOMALIES, PATIENTS WITH ESOPHAGEAL ATRESIA AND TRACHEOESOPHAGEAL FISTULA

1. Aorticopulmonary window, atrial septal defect (ASD), absent ductus arteriosus
2. Atrial and ventricular septal defects (VSD), anomalous right subclavian artery
3. Ventricular septal defect, anomalous right subclavian artery
4. Tetralogy of Fallot (ventricular septal defect, pulmonic stenosis)
5. Anomalous rotation of pulmonary artery
6. Ventricular septal defect
7. Tricuspid atresia, atrial and ventricular septal defects
8. Ventricular septal defect
9. Atrial septal defect
10. Atrial and ventricular septal defects, coarctation of aorta
11. Truncus arteriosus, ventricular septal defect, absent ductus arteriosus

VSD	8	73%
ASD	5	45%
Conotruncus anomalies	4	36%

in the Cardiac Registry of the Childrens Hospital of Los Angeles, the most frequent of a group of 4 syndromes which have in common congenital heart disease, abnormal pulmonary lobation and lobar bronchial branch-pattern, and abnormality of the spleen. Of the 18 patients in the Registry, two-thirds are male. All had, by definition of the syndrome, absence of the spleen, and all also had abnormal visceral situs and malrotation of the intestine. The typical cardiac malformation complex in this syndrome consists of common auricle and common ventricle (effectively a large ostium atrioventriculare commune), pulmonic valvular stenosis or atresia (half have each), transposition of the great arteries, anomalous pulmonary venous return (usually total), and anomalous pattern of both superior and inferior caval venous systems. Most commonly the right and left superior venae cavae drain separately into the respective atria (anatomically, both have the features of right atria), and both innominate vein and coronary sinus are undeveloped. The suprahepatic segment of the inferior vena cava is often absent, so that the hepatic veins enter the heart separately from the cava, which enters *via* the azygos vein. Dextrocardia may occur, but levocardia is more common, although two-thirds have right aortic arch. Because of the frequent occurrence of levocardia, the complex has in the past sometimes been called subdiaphragmatic situs inversus. In the CHLA series,[2] all patients with the Ivemark syndrome have symmetric lobar bronchial patterns, with an eparterial upper lobe bronchus for both lungs (pulmonary isomerism of "bilateral right lung" type). Although not pathognomonic of the Ivemark syndrome, because it also occurs in patients with situs inversus and with m-anisosplenia, the presence of a lobar bronchial pattern typical of the right lung on the left has been employed, by either contrast or air bronchography, to make or support the diagnosis of the Ivemark syndrome. The radiologic findings of this syndrome thus may include: evidence of intestinal malrotation; right-sided stomach; symmetric hepatic shadow; dextrocardia; right aortic arch; symmetric superior vena caval pattern, with the left superior cava entering the left atrium directly; transposition of the great arteries, with anteposed aortic-root, and small mediastinal vascular shadow because of the small pulmonary artery; "bilateral right lung" bronchial pattern, producing the "cow's horn" image; evidence of reduced pulmonary blood flow in the lung fields; absence of the spleen; position of the gallbladder farther to the left than normal.

The importance of the specific diagnosis of the Ivemark syndrome is largely in the evidence, supported by our own experience, that the cardiac malformation complex is not amenable to surgical treatment, and that attempts at amelioration of the cyanotic heart disease resulting from reduced pulmonary arterial flow are possibly not warranted. Patients with asplenia also appear more susceptible to severe bacterial infection than do infants with several other

similar syndromes discussed below, and a significant number of the CHLA series have died in early infancy of meningitis or other severe infection. The condition is apparently not Mendelian, we have had no instance of familial Ivemark syndrome, and parents of an infant with this disease can be counseled that the risk of recurrence of asplenia in future children is low.

POLYSPLENIA

In earlier literature often confused with the Ivemark asplenia syndrome, polysplenia is clinically, anatomically and radiologically distinct from it. In our studies we have classified the patients using the definition of polysplenia of Edwards—the presence of multiple relatively uniformly-sized small splenunculi—and have, in the Cardiac Registry, 8 patients with polysplenia. Like asplenia, the polysplenia syndrome typically produces abnormal abdominal visceral situs, with malrotation of the intestine and symmetry of the hepatic shadow. However, cardiac malformations are usually less severe than those of the Ivemark syndrome, with septal defects most common; abnormal superior and inferior caval drainage patterns are regular. Because of the better pulmonary blood flow, patients with polysplenia are typically less cyanotic than are infants with the Ivemark syndrome, and have significantly greater life span. Although the collective mass of the small spleens (we have observed from 4 to 14) is less than the normal splenic mass for the patients' ages, as supported by the observations of others that Howell-Jolly bodies occur in the red blood cells of patients with polysplenia as often as they do in patients with asplenia, the susceptibility to infection of patients with polysplenia appears to be less than that of patients with asplenia; this undoubtedly contributes to their better life expectancy.

In the CHLA series, polysplenia has occurred equally in both sexes, and all 8 patients have had pulmonary isomerism, with the bronchial pattern of the normal left lung on both sides ("bilateral left lung"). The symmetric hyparterial bronchial pattern gives, by contrast or air bronchography, a Y-shaped image (so-called inverted upsilon or inverted aries-sign pattern). The radiologic features of the polysplenia syndrome, then, may include: intestinal malrotation; symmetric liver shadow; absence of the gallbladder (apparently quite rare); abnormal caval drainage patterns; features of intracardiac septal defect; symmetrical bronchial pattern of "bilateral left lung" type. The better life expectancy and relative freedom from serious infection of patients with polysplenia, as compared to those with asplenia, make surgical attack on physiologically significant cardiac defects more justified. As with asplenia, polysplenia does not appear to be determined by a single gene abnormality, and counseling should indicate low probability of recurrence in a sibling.

F-ANISOSPLENIA

In the course of analysis of the series of patients in the files of the Cardiac Registry of the Childrens Hospital of Los Angeles, who had both congenital heart disease and abnormality of the spleen, we identified a group of patients who had multiple spleens, which were not uniform in size, as in typical polysplenia, but whose "spleen" was composed of one or more larger and one or more smaller splenunculi. This category, which we called anisosplenia, appeared to be composed of 2 distinct groups of patients: F-anisosplenia (5 patients to date) is characterized by anisosplenia, abnormal visceral situs (especially malrotation of the intestine), congenital heart disease (double outlet right ventricle was found in 3 of the 5 patients), and pulmonary isomerism of "bilateral left lung" type, with absence of the right eparterial bronchus. Although generally similar to those of polysplenia, the findings in f-anisosplenia do appear distinctive; all patients seen to date have been female, whence the name of the syndrome.

The bronchographic features of f-anisosplenia are the same as those of polysplenia,

absence of the right eparterial bronchus, with a left-lung bronchial pattern bilaterally. Both points should be established if the bronchographic findings are desired for diagnostic aid. The scimitar syndrome (see below) can produce essentially the same findings, and situs inversus causes absence of the right eparterial bronchus, but with a right-lung bronchial pattern on the left.

To date, there is no evidence that f-anisosplenia is familial.

M-ANISOSPLENIA

This malformation complex also produces pulmonary isomerism, but of right-lung type, with an eparterial upper lobe bronchus bilaterally, as in the Ivemark syndrome. Other features include congenital heart disease, especially ostium atrioventriculare commune and pulmonic stenosis, and a spleen similar to that in f-anisosplenia (1 or more larger and 1 or more smaller spleens), but essentially normal visceral situs. All 3 patients we have studied were male, whence the term m-anisosplenia. The presence of an eparterial bronchus on the left is not restricted to m-anisosplenia and the Ivemark asplenia syndrome, but is regular in situs inversus, and we have also (see below) observed it in the Ellis-van Creveld syndrome. However, bronchographic demonstration of an eparterial bronchus bilaterally would appear to permit precise diagnosis of the syndrome present, since the radiologic features of abnormal visceral situs should allow accurate separation of the asplenia from the m-anisosplenia syndromes. As far as we know, m-anisosplenia is not a familial disorder.

The significance of the sex ratios in the pulmonary isomerism—congenital heart disease—abnormal spleen complex of syndromes is uncertain, but they are of aid in diagnosis: asplenia—2/3 male; polysplenia—equal male-female ratio; f-anisosplenia—all female; m-anisosplenia—all male.

SITUS INVERSUS

This disorder, in the patients we have studied to date, also shows male preponderance; high frequency of cyanotic congenital heart disease, with pulmonary stenosis or atresia, and abnormal visceral situs, produce features of similarity to those of the Ivemark syndrome, but the reversed bronchial branch-pattern, with the eparterial bronchus on the left and a left lung pattern on the right provides a reliable diagnostic criterion.

It is important to recall that situs inversus can be, and possibly usually is, a hereditary disorder.

Adequate family studies to determine whether any of our patients may have autosomal recessive situs inversus, or the recessive Kartagener syndrome of situs inversus and chronic respiratory tract infection, with sinusitis and bronchiectasis, have not been done.

SCIMITAR SYNDROME

This disorder, named for the scimitar-shaped shadow of an anomalous pulmonary vein draining the right lung into the systemic caval system, is a familial disorder (autosomal dominant). Patients can survive to adult life, but may die in infancy or childhood with pulmonary infection. Patients with the scimitar syndrome may have either hypoplasia or absence of the right upper lobe bronchus. In the latter event, the bronchial pattern resembles that seen in polysplenia and f-anisosplenia. We have had the opportunity to study only 1 patient with this syndrome[3]—whether the bulging appearance of the upper lobe bronchus at the normal site of origin of the eparterial bronchus reliably permits bronchographic recognition of the scimitar syndrome in childhood we cannot say.

ELLIS-VAN CREVELD SYNDROME

This well-known hereditary disorder includes skeletal dysplasia with short-limbed dwarfism, ectodermal dysplasia, and congenital heart disease. As in a number of other chondrodystrophies, there is abnormality of the tracheobronchial cartilages, with narrowing of the tracheal and bronchial air-columns. In the 1 patient we have studied there was also an eparterial bron-

chus on the left. Whether patients with Ellis-van Creveld syndrome have pulmonary isomerism of bilateral right lung type, or reversed major bronchial pattern, or both, the frequency of either, and the possible diagnostic value of demonstration of the bronchial branch pattern in the separation of the Ellis-van Creveld syndrome from other hereditary chondrodystrophies requires further study.

RETROTRACHEAL (SLING) LEFT PULMONARY ARTERY

The radiographic features of this disorder, also known as origin of the left pulmonary artery from the right, in which the left pulmonary artery passes to the right of the lower trachea and then runs between the trachea and esophagus to the left lung, are well known. Respiratory problems attributed to tracheal narrowing are frequent in patients with this disorder, and may, but by no means always do, respond to surgical treatment. One reason for this is the high frequency of association of ring tracheal cartilages ("napkin-ring" tracheal cartilages, absence of the pars membranacea of the trachea) with sling left pulmonary artery—present evidence is that about 50 per cent of patients with the vascular anomaly have the tracheal lesion. Absence of the posterior tracheal membrane, the pars membranacea, typically causes exaggerated narrowing of tracheal diameter from superior to inferior ("carrot-shaped trachea"), with functional tracheal stenosis in some patients. Surgical treatment is theoretically possible, but we have no experience with it. At any rate, it would seem warranted, before operation on a patient with sling left pulmonary artery and respiratory difficulty, to establish, by endoscopy or bronchography, whether the patient appears to have ring tracheal cartilages, because this lesion may be more responsible for the respiratory difficulty than compression of the lower trachea or major bronchi by the anomalous artery.

LOBAR EMPHYSEMA

Deficiency of bronchial cartilage plates, with obstructive emphysema because of bronchial or bronchiolar buckling on expiration, appears to be the mechanism of lobar emphysema. In a recently reported series of patients with this disorder, from our hospital,[1] 6 of 16 patients with lobar emphysema also had congenital heart disease. As Table III shows, patent ductus arteriosus was the most common cardiovascular lesion in the patients with lobar emphysema. The spectrum of cardiac anomalies in this group differs from that seen in association with EA-TEF, for example, as well as from that seen in association with asplenia, polysplenia, f-anisosplenia, situs inversus, and Ellis-van Creveld syndrome. Whether the association of cardiac malformation with adenomatous dysplasia of the lung is significant or repetitive, and of predictive value, requires further study.

Table III

CARDIAC MALFORMATIONS IN PATIENTS WITH LOBAR EMPHYSEMA OR ADENOMATOUS DYSPLASIA OF LUNG

Lobar emphysema (6 of 16)
patent ductus arteriosus—3
atrial septal defect, ? truncus arteriosus *vs.* patent ductus arteriosus—1
aortic stenosis—1
pulmonic stenosis—1
Adenomatous dysplasia (cystic adenomatoid malformation) (4 of 19)
dextrocardia—1
ventricular septal defect—1
patent ductus arteriosus—1
multiple intracardiac defects—1

Table IV summarizes the cardiac malformations in the 10 syndromes discussed in this paper—syndromes of tracheobronchial anomaly with congenital heart disease. As can be seen, direct radiologic demonstration of these tracheobronchial anomalies is possible, except for lobar emphysema, where the emphysema is distinctive, but provides only indirect evidence of the bronchial cartilage deficiency. Radiologic demonstration of these tracheobronchial lesions can be of definite diagnostic and predictive value, and lead to both improved treatment of affected pa-

TABLE IV

SYNDROMES OF TRACHEOBRONCHIAL ANOMALY WITH CONGENITAL HEART DISEASE

Syndrome	Tracheobronchial lesion	Most typical cardiac lesions
1. ARTICLE complex	EA-TEF	ASD, VSD, conotruncal anomalies
2. Asplenia (Ivemark syndrome)	Pulmonary isomerism (bilateral right lung type)	Common auricle and ventricle, PS or PA, transposition, TAPVR
3. Polysplenia	Pulmonary isomerism (bilateral left lung type)	Septal defects
4. f-anisosplenia	Pulmonary isomerism (bilateral left lung type)	DORV
5. m-anisosplenia	Pulmonary isomerism (bilateral right lung type)	Various
6. Situs inversus	Reversed lobar bronchial pattern	PS or PA, septal defects, dextrocardia
7. Scimitar syndrome	Absence or hypoplasia, right upper lobe bronchus	Anomalous arterial and venous supply, right lung
8. Ellis-van Creveld syndrome	Abnormal tracheal and bronchial cartilages, airway narrowing, ? pulmonary isomerism *vs.* reversed bronchial pattern	ASD
9. Sling left pulmonary artery	Tracheal stenosis due to ring tracheal cartilages	Sling left pulmonary artery
10. Lobar emphysema	Bronchial cartilage plate deficiency	PDA, AS, PS

EA-TEF = esophageal atresia with tracheoesophageal fistula; ASD = atrial septal defect; VSD = ventricular septal defect; PS = pulmonic stenosis; PA = pulmonary atresia; TAPVR = total anomalous pulmonary venous return; DORV = double outlet right ventricle; AS = aortic stenosis; PDA = patent ductus arteriosus.

tients and improved counseling of their families.

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TRACHEOBRONCHIOMEGALY IN AN 18 MONTH OLD CHILD*

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TRACHEOBRONCHIOMEGALY is a disorder of unknown etiology characterized by prominent dilatation of the trachea and main stem bronchi. Since its first clinical description in 1932 by Mounier-Kuhn,[7] it has been increasingly reported and is now a well-recognized, albeit rare, pathologic entity. Until 1962 when Katz *et al.*[6] in their definitive review of the disease introduced the term tracheobronchiomegaly, it had been called by a variety of terms, including Mounier-Kuhn syndrome, tracheal diverticulosis, tracheobronchiectasis, tracheocoele, tracheomalacia, trachiectasis, megatrachea, and tracheobronchiopathia malacia.[6,8] Most authors now prefer the term tracheobronchiomegaly because of its very descriptive nature. In 1973 when Bateson and Woo-Ming[2] reported 2 cases, they found a total of 55 cases published in the literature up to that time, the majority of whom involved males in the third and fourth decades. A few cases have been reported in children and elderly persons.

The clinical symptomatology associated with tracheobronchiomegaly is similar to that found in persons with chronic respiratory infections. Cough, recurrent fevers, sputum production and even cyanosis, finger clubbing, and frank pulmonary consolidation can be seen. Dyspnea may or may not be present.[2,6] The duration of symptoms is usually long, often as far back as early childhood.[6] Quite frequently the patients have an associated chronic respiratory tract inflammatory disease, particularly bronchiectasis. The basic pathologic mechanism is probably a defect in the elastic and muscular tissues of the trachea and main bronchi.[6] This results in marked enlargement of these structures during quiet breathing or inspiration and a tendency toward total collapse upon expiration. As a result there is an enlarged dead space, increased tidal volume, and poor clearing of secretions.[2] There may be, in addition, redundant folds of mucous membrane and large outpouchings of the tracheal wall due to its intrinsic structural weakness.

Although patient symptomatology often dates back to childhood, the condition has very rarely been documented in children. As far as we have been able to ascertain, the youngest reported patient has been an 8 year old.[3] We would like to report typical roentgenographic features of this disease in an 18 month old child and emphasize that greater familiarity with its roentgenographic characteristics may lead to its being more commonly recognized in patients of all ages, especially children.

REPORT OF A CASE

S.V.H., an adopted Black female, had a normal birth and postnatal course. Her natural parents were said to be in good health. Her growth and development were normal during the first year. At age 14½ months she was treated for a right middle lobe pneumonia which subsequently resolved. At 16 months of age she presented with a cough of 2 weeks' duration without fever. Her mother also described the child as having a constant "rattle in the throat." Examination then revealed a child in no distress but whose noisy respirations could be "heard in the next room." She was not hoarse but had a brassy, almost croup-like cough. Auscultation revealed only coarse rhonchi. A chest roentgenogram at this time raised

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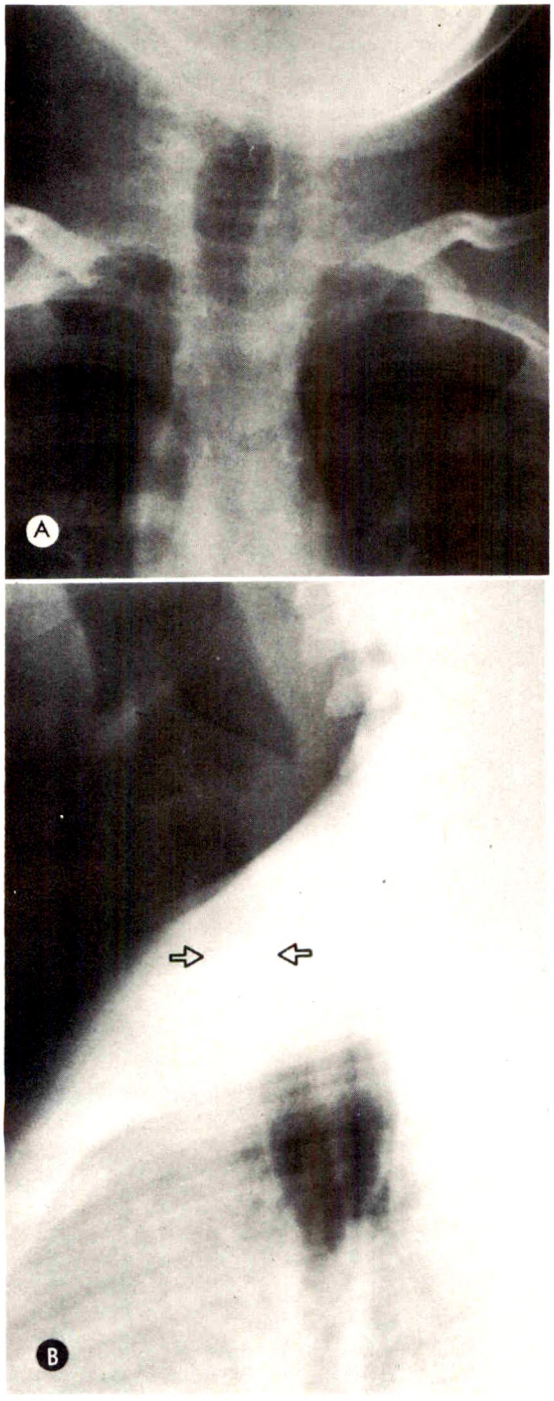

Fig. 1. An 18 month old female. (*A*) Anteroposterior view of the trachea during phonation on routine chest roentgenogram. Note the marked saccular dilatation of the trachea and the close approximation of the tracheal width to that of a cervical vertebral body. (*B*) Lateral view during crying on routine chest roentgenogram. Again noted is the marked dilatation of the trachea, especially the proximal portion (arrows).

the question of small pleural effusions and the patient was placed on antibiotics. A sweat chloride test was normal.

Because the patient's findings were not relieved by either antibiotics or bronchodilators, a repeat chest roentgenogram was obtained 2 months later when the child was 18 months of age (Fig. 1, *A* and *B*). Prominent dilatation of the trachea in both the frontal and lateral views was noted. There was no evidence of other abnormalities. This dilatation could retrospectively be noted on the previous roentgenograms. Fluoroscopy of the chest with videotape recording and 70 mm. spot filming was then performed. This demonstrated further increase in the tracheal dilatation with inspiration and almost complete tracheal collapse with expiration (Fig. 2, *A* and *B*). When a nasogastric tube was used to stimulate the nasopharynx and induce coughing, tracheal collapse was again noted. One of the authors (J.F.H.) is familiar with the typical roentgenographic and fluoroscopic picture of tracheobronchiomegaly, having seen several cases in adults previously reported[5] and believes that the roentgen studies in this child are diagnostic of this condition.

When the patient was last seen at 20 months of age, her physical examination and growth were normal. There has never been any evidence of a generalized connective tissue disorder. She is to be followed periodically by her pediatrician (M.A.R.) and treated symptomatically as her condition warrants. No further roentgen studies are anticipated at this time.

DISCUSSION

Tracheobronchiomegaly is usually diagnosed by its radiologic appearance.[2,6,8] On standard frontal and lateral chest roentgenograms the trachea is markedly dilated (Fig. 1). The width of the tracheal air column may equal that of the thoracic vertebral column.[2,5,6,8] This dramatically increased tracheal width should not be confused with the slender, uniform widening seen in pulmonary fibrosis or the mild tracheal and bronchial dilatation noted in patients with chronic cough, bronchiectasis, or occupations entailing excessive vocal or pulmonary effort.[6] Fluoroscopically, tracheobronchiomegaly typically demonstrates gigantic expansion of the trachea and sometimes the major bronchi during inspiration and complete collapse with

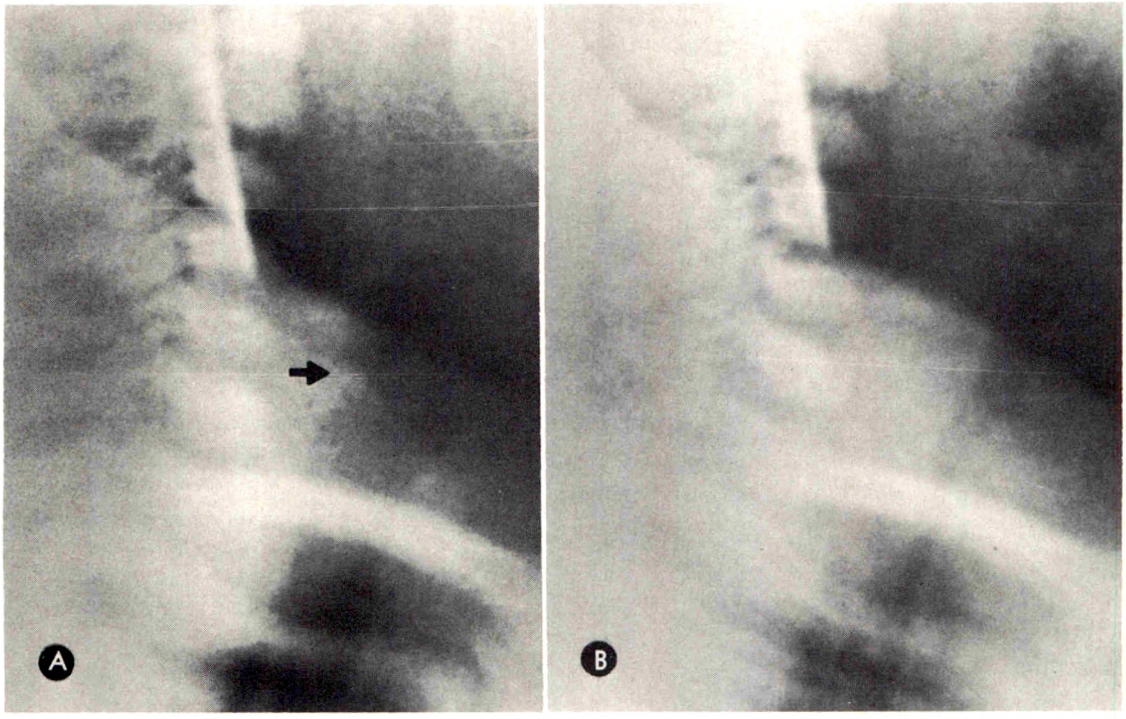

Fig. 2. (*A*) A 70 mm. spot film of upper trachea showing infolding of the mucosa during inspiration (arrow). (*B*) A 70 mm. spot film of upper trachea showing almost complete tracheal collapse during coughing induced by a nasopharyngeal feeding tube.

expiration or coughing (Fig. 2). Bronchography may reveal bulging of the tracheal lumen between the tracheal cartilage rings producing multiple "diverticula." This is stated to be present in one-third of the cases.[2] Bronchography can also show associated bronchiectasis and other chronic inflammatory changes.

Bronchoscopy may aid in the diagnosis by showing an enormous tracheal lumen. There may be a nonresistant obstruction caused by the redundant tracheal wall in a collapsed state. Semicircular folds of mucous membrane and saccular pouches may also be noted.[2,6]

The incidence of tracheobronchiomegaly is unknown, although it may be more common than generally thought. Himalstein and Gallagher[4] diagnosed the condition in approximately 1 per cent of their bronchograms performed in adults. Most authors ascribe the condition to a congenital defect in development of the connective tissue elements in the walls of the trachea and main stem bronchi. Support for this theory is derived from the frequent history of symptoms dating to childhood, histologic studies showing poorly developed elastic and muscular tissue, and the rarity of the process in comparison to the relative commoness of chronic inflammatory respiratory tract disease.[2,6] Moreover, tracheobronchiomegaly has been reported in connection with acquired cutis laxa in a child and Ehlers-Danlos syndrome in an adult.[1,8] Johnston and Green,[5] in their description of 5 patients showed a familial occurrence and discussed data suggesting an autosomal recessive type of inheritance. Bateson and Woo-Ming[2] feel there may be a racial predisposition in Blacks.

It is difficult, nevertheless, to ascribe all aspects of this condition to a congenital process. The vast majority of patients are adults at the time of diagnosis and even though they give a long history of symptoms, the condition has rarely been documented in childhood. Approximately 75

per cent of the reported cases have been in persons over the age of 29.[2] The rather close association between chronic respiratory diseases and tracheobronchiomegaly may be indicative of a common etiologic cause, with infectious processes in certain predisposed individuals giving rise to the typical picture of tracheobronchiomegaly over a period of some years. Certainly, the condition's etiology remains unexplained.

Our patient is of particular interest because of her young age at presentation. This occurrence so early in life appears to support the concept of a congenital defect in development of connective tissue elements. Adult measurement standards for tracheal size are not readily applicable to pediatric patients, but pediatricians and radiologists should become more alert to the possibility of tracheobronchiomegaly occurring during childhood. Dilatation of the trachea equal to or greater than the width of a thoracic vertebral body is highly suggestive of the condition. Fluoroscopy of the trachea during inspiration, expiration, quiet breathing, phonation and vigorous coughing can be used to confirm the diagnosis. Recording tracheal and bronchial dynamics with cine or on videotape is especially useful. Ordinarily, bronchography and bronchoscopy will not be needed and may even be detrimental to a young patient. As pediatricians and radiologists become more familiar with the disease, we believe it will be recognized more frequently and this will lead to a fuller understanding of its causes and clinical course.

SUMMARY

Tracheobronchiomegaly occurring in an 18 month old child is reported.

The etiology, clinical course, and roentgenologic manifestations of tracheobronchiomegaly are discussed.

It is postulated that this rare condition may be more frequently diagnosed as pediatricians and radiologists become more aware of its possible presentation during childhood.

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ROENTGENOGRAPHIC AND ANGIOCARDIOGRAPHIC CHANGES AFTER TOTAL CORRECTION OF THE TETRALOGY OF FALLOT*

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TOTAL surgical correction has become a well established and successful treatment for the Tetralogy of Fallot since Lillehei *et al.*[16] first performed this procedure in 1955. Despite the highly satisfactory clinical results and the ever decreasing mortality,[8] postoperative cardiac catheterizations may show residual hemodynamic abnormalities and angiography may reveal residual anatomic abnormalities. These residual postoperative changes may occur in both patients with clinically acceptable results and those with poor results.

In this paper, the postoperative roentgenographic and angiocardiographic changes after total surgical correction for the Tetralogy of Fallot will be analyzed. These findings will be correlated with the type of operative procedure performed and hemodynamic data.

MATERIAL AND METHOD

Pre- and serial postoperative thoracic roentgenograms were available for study on 108 patients who had undergone correction of the Tetralogy of Fallot at the University of Minnesota Hospitals. Each of these patients had preoperative angiograms, and 66 patients had postoperative angiograms available. Postoperative right heart catheterization was performed in each of the 108 patients.

Sixty-eight patients were males, and 40 were females. At the time of corrective surgery, 80 patients were less than 5 years of age; and 28 ranged from 5 to 19 years of age. From 8 months to 10 years following the first operation, 17 patients had undergone a second operative procedure for correction of residual abnormalities such as ventricular septal defect, right ventricular outflow tract obstruction and aneurysm of the outflow tract.

The postoperative thoracic roentgenograms were available for periods of 1 to 10 years after corrective operation (1–2 years: 44 patients; 2–5 years: 37 patients; 5–10 years: 16 patients; over 10 years: 11 patients). Thoracic roentgenograms from the immediate postoperative period were not studied because of the many transient changes seen. There were a total of 76 postoperative angiographic studies; 10 of these being performed after a second operative intervention for total correction. Fifty-nine studies were performed within 2 years of operation; 14 studies at 2–5 years; 1 study at 5–10 years; 2 studies at 10 years.

RESULTS

THORACIC ROENTGENOGRAMS

Thoracic roentgenograms were evaluated for cardiac size, pulmonary vasculature, and the appearance of the cardiac contour.

Cardiac Size. Cardiac size and changes following surgery were measured using the cardiothoracic ratio (CTR). The mean cardiothoracic ratios increased significantly ($p<0.01$) from a preoperative value of 0.48 ± 0.005 to a postoperative value of 0.53 ± 0.007.

By 6 to 12 months after operation, the cardiac size was either stable or had decreased slightly. The only exceptions were patients with severe hemodynamic changes resulting from residual ventricular septal defect or right ventricular aneurysm. In these, progressive cardiomegaly occurred.

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TABLE I

POSTOPERATIVE CARDIOTHORACIC RATIO

Cardiothoracic Ratio	No. of Patients	Per Cent of Total
<0.50	40	37
0.51–0.60 (mild cardiomegaly)	57	52.8
0.61–0.70 (moderate cardiomegaly)	6	5.6
>0.71 (marked cardiomegaly)	5	4.6
Totals	108	100.0

Among the total of 108 patients studied, there were 16 patients who had previously undergone systemic-pulmonary arterial shunt procedure and/or Brock valvotomies. The mean value (0.52) of the CTR for this group was significantly different ($p<0.005$) from the value (0.48) of the CTR for the group without shunts prior to total correction.

A tabulation of the degree of cardiomegaly found in the postoperative thoracic roentgenogram is found in Table I. In each case with marked cardiomegaly (CTR >0.71), major postoperative complications were present. These included atrioventricular dissociation, postoperative false aneurysm of the right ventricular outflow tract, operative ligation of a coronary artery or marked cardiomegaly preoperatively.

In patients with CTR <0.70, there was no significant correlation between the postoperative CTR and the peak right ventricular systolic pressure, size of residual shunt, or the gradient across the outflow tract. The CTR could not be correlated with the presence of an outflow patch.

Pulmonary Vasculature. The pre- and postoperative appearance of the pulmonary vasculature is presented in Table II. Whereas preoperatively, half the patients had decreased blood flow, all postoperative roentgenograms showed normal or increased flow.

Cardiac Contour. The most constant postoperative change was the filling-in of the region of the pulmonary outflow tract. This occurred in each patient (Fig. 1, *A* and *B*). This area was particularly prominent following extensive infundibular muscle resection or pulmonary arterial reconstruction. It was not always possible to determine from the thoracic roentgenogram if this prominence was related to aneurysmal dilatation of the outflow tract or to a dilated pulmonary trunk secondary to pulmonary valvular insufficiency. The appearance of a "prominent outflow tract" may be caused by a dilated left pulmonary artery as it arches over the left main stem bronchus overlapping the pulmonary trunk and giving a "dilated" or "prominent" appearance to this area.

Three cases showed rim-like calcifications in the outflow tract patch: 2 in Ivalon patches and 1 in a pericardial patch. Although in this series teflon was used as frequently as pericardium and more than Ivalon, there were no cases of calcification in teflon patches.

TABLE II

APPEARANCE OF PULMONARY VASCULATURE

Patient Status	Decreased		Normal		Normal*		Increased		Total	
	No. of Patients	Per Cent	No. of Patients	Per Cent	No. of Patients	Per Cent	No. of Patients	Per Cent	No. of Patients	Per Cent
Preoperative	51	47	36	33	19	18	2	2	108	100
Postoperative	0	0	80	74	0	0	28	26	108	100

* Normal (↓ left upper lobe vasculature).

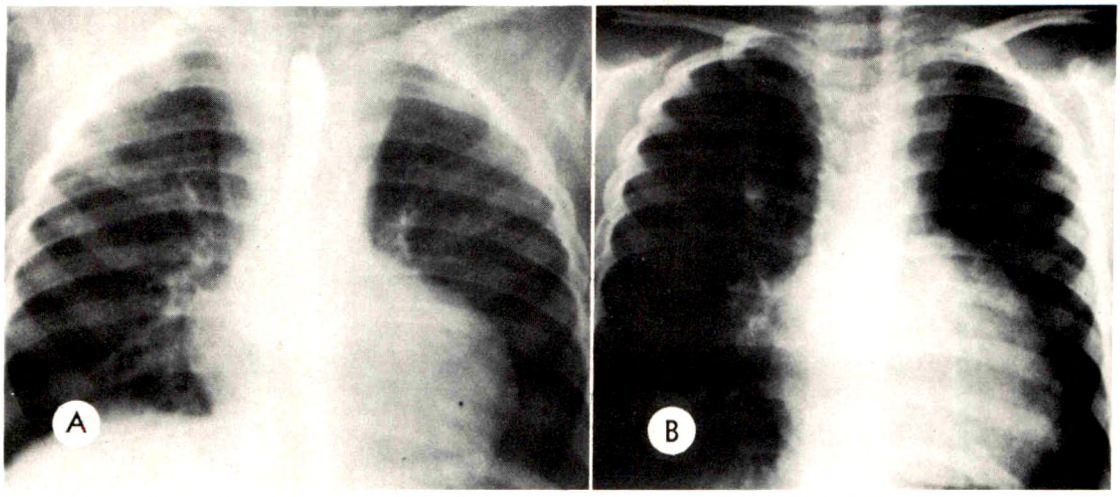

FIG. 1. Pre- and postoperative appearance of the pulmonary outflow area. (*A*) Preoperative chest roentgenogram. Heart size normal and boot-shaped, concave main pulmonary artery segment. (*B*) Postoperative chest roentgenogram. Increased heart size, filling-in of the main pulmonary artery segment which now appears fairly prominent.

The type of ventriculotomy (whether vertical or horizontal) and the type of patch material did not appear to bear directly on the degree of prominence of the outflow tract observed postoperatively.

ANGIOCARDIOGRAPHIC FINDINGS

The postoperative right ventriculograms were analyzed for: (1) residual ventricular septal defect and appearance of the ventricular septal patch; (2) appearance of the right ventricular cavity; (3) right ventricular outflow tract (width and motion of infundibulum, outflow tract patch, aneurysm of outflow tract); (4) residual pulmonary valvular stenosis; and (5) main pulmonary artery and branches.

Ventricular Septum. A residual ventricular septal defect was observed on right ventriculography in 26 patients, although 8 of these were not detected by oxymetry data. The defect was visualized either as a well defined small jet directed posteriorly across the septum or as contrast material spilling into the left ventricular chamber below the aortic valve. In most instances the defect was located along the superoposterior aspect of the ventricular septal defect patch site. A grossly detached patch was seen in 3 cases as a wide, irregular radiolucency moving between the ventricles. The detachments occurred in the superoposterior aspect of the patch.

From the left ventricular aspect, the patch over the ventricular septal defect appeared as an outpouching into the right ventricular outflow tract or as an irregular area on the right ventricular aspect of the septal wall (Fig. 2, *A* and *B*).

Outflow Tract of the Right Ventricle. Each of the 76 postoperative ventriculograms showed widening of the infundibular region. The type of operative procedure performed to enlarge the outflow area influenced the postoperative appearance of this region.

(1) Infundibulectomy and resection of infundibular muscle was performed in 38 patients. In 5 of these patients aneurysms of the outflow tract were present, with 2 aneurysms being present in 1 of these (both a true and a false aneurysm were present and diagnosed at surgery).

The true aneurysms were located along the anterior and left lateral aspect of the right ventricular outflow area (Fig. 3, *A* and *B*). One showed paradoxical motion and a narrow neck, while the other 2 were akinetic and had wide necks. One of the false aneurysms extended posteriorly to the area immediately below the main pulmo-

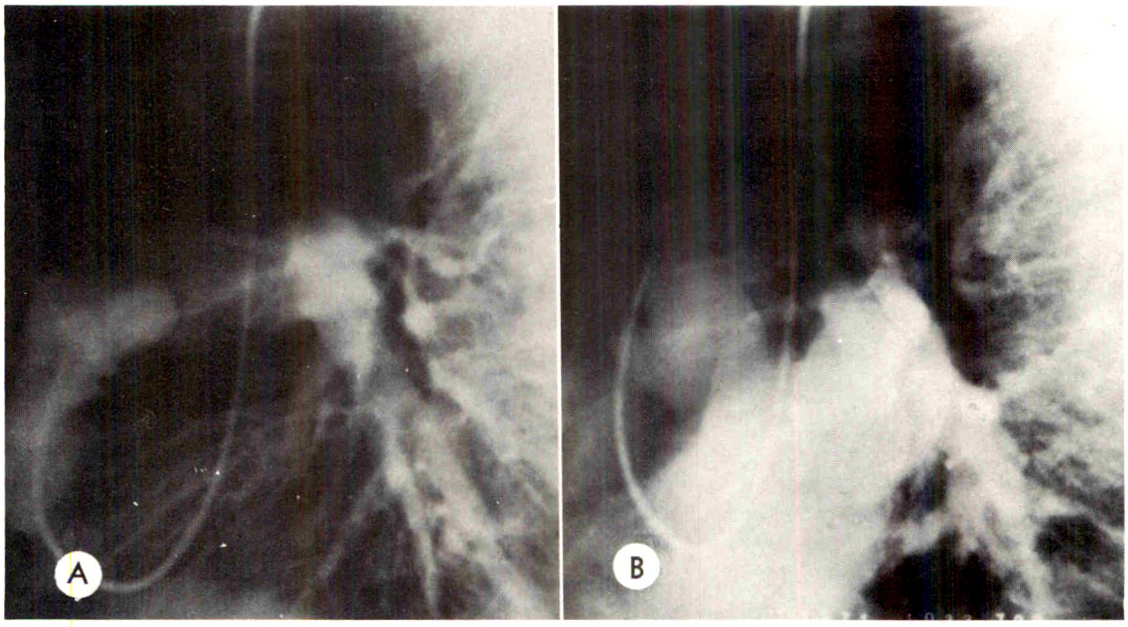

Fig. 2. Postoperative appearance of a ventricular septal defect patch. (*A*) Right ventriculogram. Irregular appearance of the posterior aspect of the wide infundibulum. (*B*) Levophase. Patch appears as an outpouching into the right ventricular outflow tract. Left-to-right shunt: 45 per cent.

nary artery and communicated with the outflow tract via a long tract; its walls were akinetic. A second false aneurysm showed an akinetic, bilobed appearance on the left lateral aspect of the outflow tract. A third false aneurysm was located to the left and anterosuperiorly to the outflow tract with which it communicated (Fig. 4, *A–C*). This same patient also had a true aneurysm of the outflow tract at the site of the ventriculotomy line.

Seven patients showed a bizarre appear-

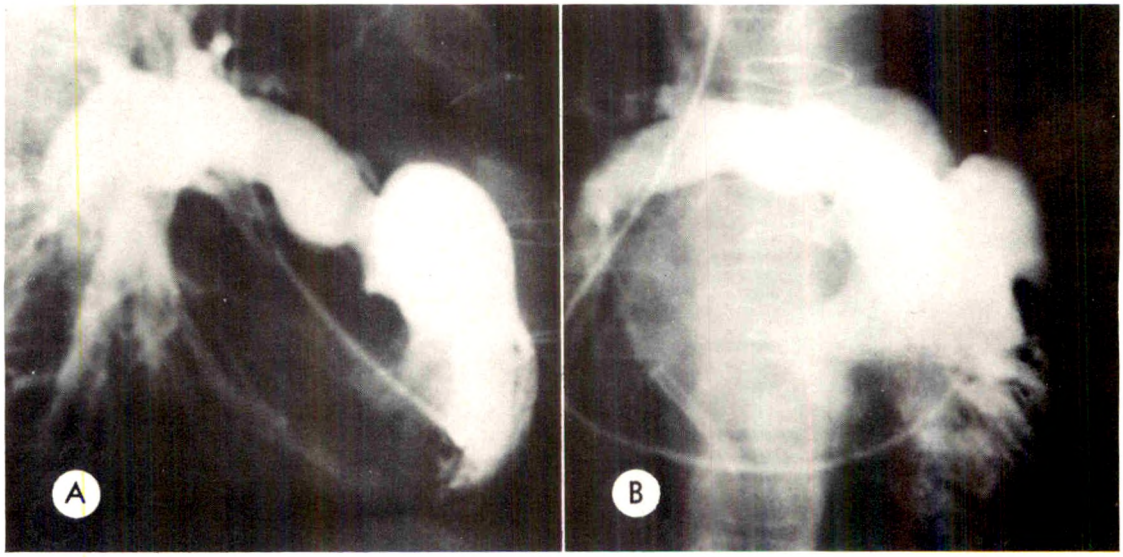

Fig. 3. (*A* and *B*) True aneurysm of the outflow tract. (*B*) Aneurysmal outpouching located along the left lateral aspect of the outflow tract has narrow neck, paradoxical motion and smooth margins. RV/PA gradient: 16 mm. Hg.

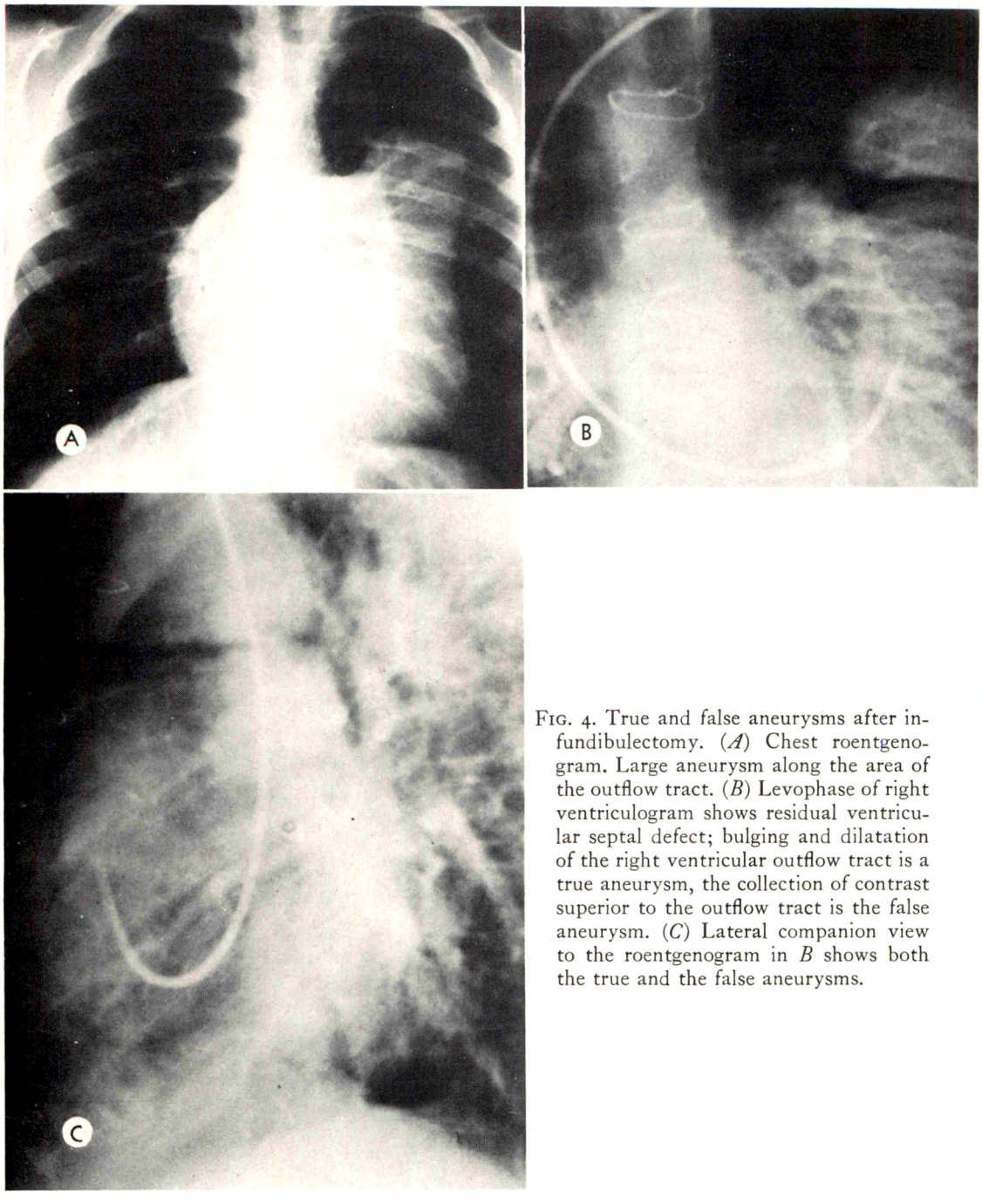

Fig. 4. True and false aneurysms after infundibulectomy. (*A*) Chest roentgenogram. Large aneurysm along the area of the outflow tract. (*B*) Levophase of right ventriculogram shows residual ventricular septal defect; bulging and dilatation of the right ventricular outflow tract is a true aneurysm, the collection of contrast superior to the outflow tract is the false aneurysm. (*C*) Lateral companion view to the roentgenogram in *B* shows both the true and the false aneurysms.

ance of the outflow tract after infundibulectomy. Four had a localized area of hypokinesia or akinesia along the ventriculotomy line in the presence of an otherwise acceptable hemodynamic result (Fig. 5, *A* and *B*). Three showed adhesions of the anterior aspect of the right ventricular outflow tract to the sternum. That portion of the outflow tract adherent to the sternum was akinetic (Fig. 6, *A* and *B*).

(2) Patch reconstruction of the outflow tract was done in 13 cases. Postoperatively, the anterior aspect of the outflow tract appears widened and noncontractile. The in-

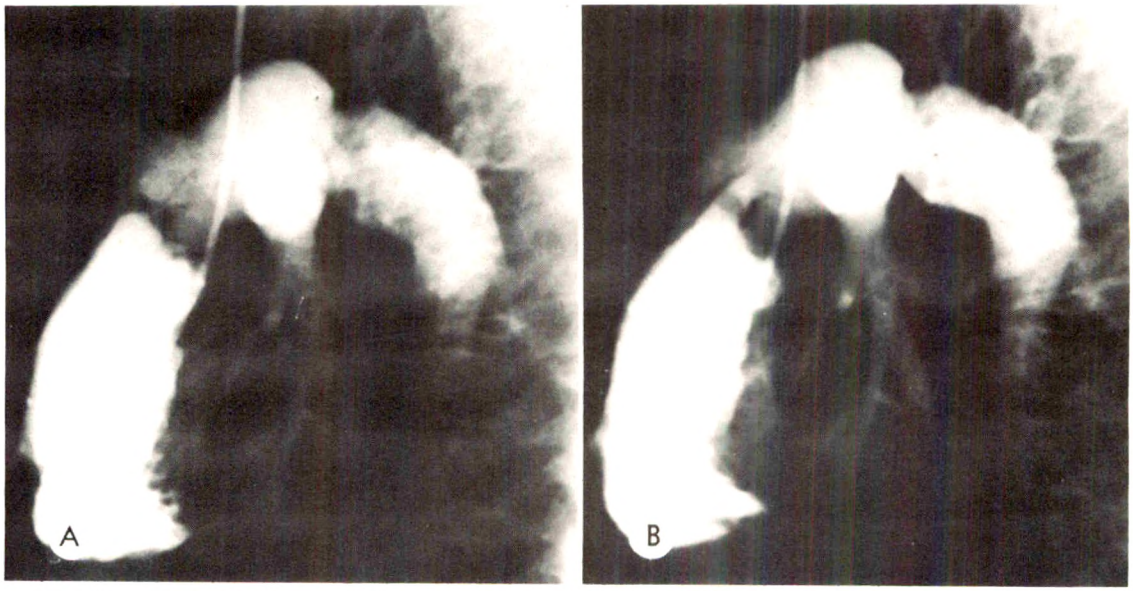

FIG. 5. (*A* and *B*) Lateral views of a right ventriculogram after infundibulectomy. Irregular appearance and bizarre motion of the anterior aspect of the ventricular wall.

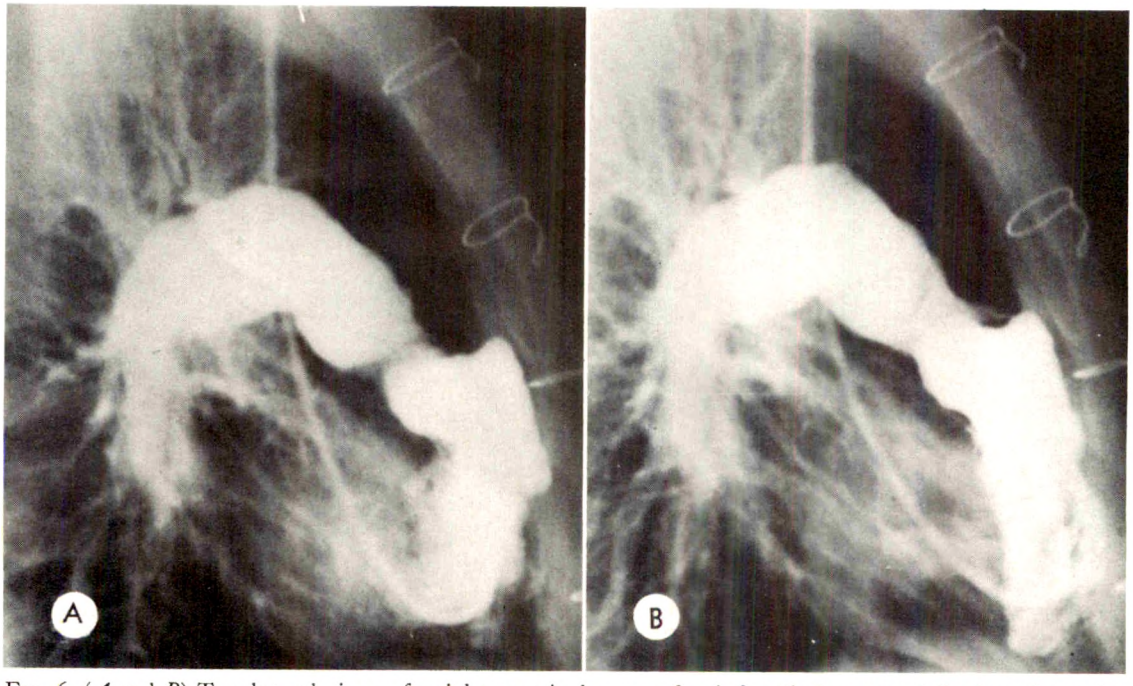

FIG. 6. (*A* and *B*) Two lateral views of a right ventriculogram after infundibulectomy. Adhesion of anterior aspect of outflow tract to posterior aspect of sternum. The area appears immobile and fixed to sternum.

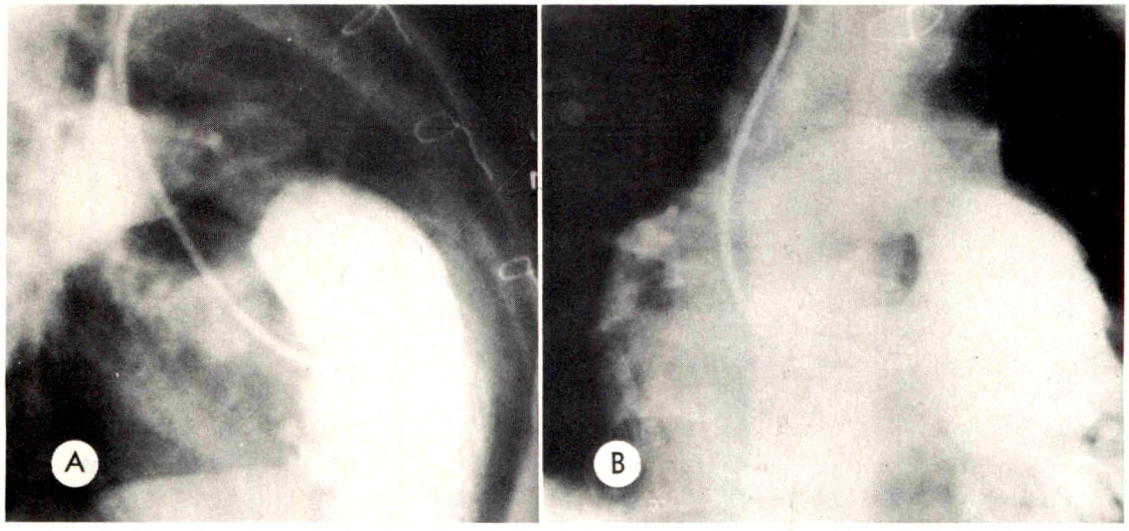

Fig. 7. Postoperative appearance of outflow tract after reconstruction with pericardial patch. (*A*) Lateral and (*B*) anteroposterior views of a right ventriculogram. Dilatation of the outflow tract of the right ventricle extends up to the annulus. Patch area of outflow tract appears smooth on lateral view and slightly irregular on anteroposterior view. Small ventricular septal defect seen. At catheterization there were mild pulmonary stenosis and insufficiency.

ferior aspect of the patch is recognized by a sudden anterior protrusion at the site, where the patch has been sutured to the ventricular wall. Some dilatation and irregularity at the patch site was always seen (Fig. 7, *A* and *B*).

(3) Twenty-five patients had outflow tract patch reconstruction with extension of the patch across the annulus. Ten of these patients showed marked dilatation of the pulmonary trunk and outflow tract (Fig. 8, *A* and *B*), while in the other fourteen the outflow tract area appeared normal or only slightly prominent. Each of the 10 cases with marked outflow tract dilatation showed obvious pulmonary insuffi-

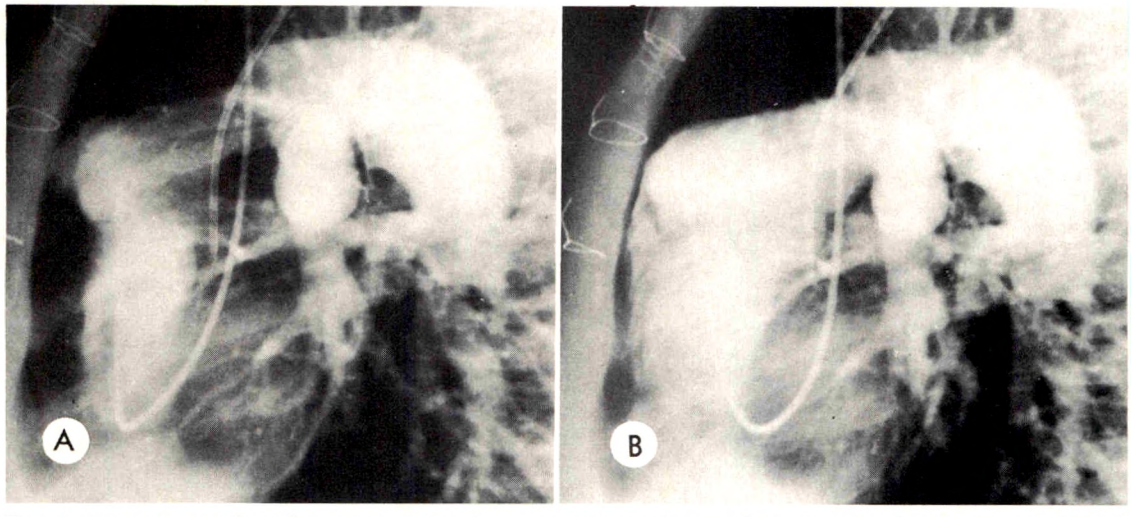

Fig. 8. Appearance of outflow tract and pulmonary artery after outflow tract patch reconstruction with extension of the patch across the pulmonary annulus. (*A* and *B*) Two lateral views of right ventriculogram. The outflow tract is wide as are the pulmonary annulus and pulmonary artery. At cardiac catheterization there was moderate pulmonary insufficiency. RV/PA gradient: 30 mm. Hg.

ciency. Three of these 25 patients showed aneurysms of the outflow tract.

Pulmonary Valve. Residual pulmonary valvular stenosis was present angiographically in 25 cases but appeared nonstenotic in the other 5. In only 4 patients was infundibular stenosis apparent angiographically.

No correlation was found between the angiographic appearance of the infundibulum and pulmonary valve and the degree of valvular or infundibular stenosis found at cardiac catheterization.

Main Pulmonary Artery and Its Branches. The postoperative appearance of the main pulmonary artery was dependent upon the preoperative appearance and the type of operative procedure. In 25 patients, the patch was extended across the annulus; and of these, 10 showed marked dilatation of the outflow tract and pulmonary artery. In the other 15 with a patch across the annulus, the outflow tract appeared normal.

There were other patients with abnormalities of the pulmonary arterial tree. One showed stenosis at the distal aspect of the graft and another showed kinking or buckling of the inferior aspect of the main pulmonary artery at the distal border of graft. Two patients had stenosis of the origin of the right pulmonary artery preoperatively; the postoperative angiogram showed no postoperative change in one and progression of the poststenotic dilatation in the other. Two patients with peripheral artery stenosis did not show any change of these lesions in the postoperative angiogram.

DISCUSSION

Most patients with Tetralogy of Fallot can be anatomically corrected by cardiac surgery with low operative mortality,[8,11,14,15,18] and the anticipation of improved cardiac status.[1–3,5,15,17,21,23] Although the postoperative clinical status of the patients may be excellent in the majority of patients,[15] some have residual abnormal hemodynamics which require close clinical follow-up and even a second operative procedure. It would be helpful if the clinical findings could predict which patients had major residual abnormalities following operation. In this study, we had hoped that thoracic roentgenographic and angiographic changes could be correlated well with the postoperative hemodynamic abnormalities. However, no significant correlations were found.

After the immediate postoperative period, the change most often noted in the thoracic roentgenogram is an increase in cardiac size.[4,9,22] This change may be slight or marked, but only 8 of our cases failed to show it. This increase apparently occurs within the first 6 postoperative months, since it was always present 6 to 12 months after surgery. In the presence of a good hemodynamic result, the postoperative cardiac size remained stable. Progressive increase in cardiac size after the first 6 months indicates a significant hemodynamic problem such as re-opened ventricular septal defect, significant residual outflow tract obstruction, outflow tract aneurysm, severe pulmonary insufficiency, atrioventricular dissociation, complete heart block, postsurgical coronary artery abnormalities or a combination of these.

Some authors indicate that the cardiac size of patients with patches across the pulmonary annulus tends to be larger than among patients without such a patch, perhaps because of the pulmonary insufficiency which the procedure creates.[7] Both Kirklin *et al.*[15] and Gersony *et al.*[8] found the CTR to be larger in patients with outflow tract patches. Among our postoperative patients, the cardiac size did not show any correlation with patching of the outflow tract and whether the patch extended across the annulus or not.

Postoperatively increased prominence of the right ventricular outflow tract area was noted in each of our cases and has been previously described.[4,7,22] The degree of prominence observed in the groups with outflow tract reconstruction was no greater

than in patients with only an infundibulectomy. The type of ventriculotomy, whether horizontal or vertical, also did not influence the degree of outflow tract prominence. It is difficult to distinguish from the thoracic roentgenogram alone whether the prominence is related to dilatation of the outflow tract secondary to marked pulmonary insufficiency, dilatation of the patch in the outflow tract, or an aneurysm of the outflow tract. To diagnose postoperative outflow tract aneurysm, clinical findings, serial roentgenograms, and even re-catheterization and angiocardiography may be necessary.

There was no correlation between the degree of postoperative cardiomegaly or the degree of prominence of outflow tract and the following hemodynamic parameters: peak right ventricular systolic pressure; size of the residual shunt; or residual gradient across the right ventricular outflow tract. For any one particular case, 1 of these factors may be related to postoperative cardiomegaly, for example, a residual ventricular septal defect in the presence of complete relief of the right ventricular outflow obstruction. However, in most cases, an abnormal degree of cardiomegaly is caused by a combination of these factors rather than by 1 particular factor.

Linear calcification in prosthetic materials used for reconstruction of the right ventricular outflow tract has been reported in various series.[7,12,13,19] Although most commonly present in Ivalon patches, it has been also reported in pericardial patches but not in teflon patches. In our 3 cases of calcification, 2 occurred in an Ivalon and 1 in a pericardial patch.

The incidence of residual ventricular septal defect varies widely among the reported series and appears to depend on the type of diagnostic method used in evaluating for residual shunt. Malm and associates[18] followed 100 consecutive postoperative patients: 64 were catheterized; and of these, 9 (10.9 per cent) had left-to-right shunts by oxymetry. Burnell *et al.*[5] found 3 residual ventricular shunts among 13 cases (23 per cent); 1 of these was detected by hydrogen indicator technique only. Kirklin and co-workers[15] found residual or recurrent ventricular shunts in only 8 of 92 patients (8 per cent) in whom a patch had been used to close the ventricular septal defect. Lillehei and his group[16] found 15 residual shunts in 30 patients (50 per cent), but these were done early in the experience of total correction and many of the ventricular septal defects were closed by direct suture technique rather than with a patch.

In our group, 26 of 65 patients (40 per cent) undergoing right ventricular angiography showed a residual ventricular septal defect. Eight of these were not detected by oxymetry and were seen only transiently during angiography, and 4 were less than 20 per cent left-to-right shunts. Of the group of 108 patients included in this study, 40 (37 per cent) had residual shunts. The more common site of recurrence was at the superoposterior aspect of the patch. This is in contrast to the series of Malm *et al.*[18] in which most of the ventricular septal defects were in the inferoposterior aspect of the ventricular septal patch. A difference in operative technique may explain this discrepancy.

Angiographic abnormalities in the outflow tract occurred secondary to the following factors: ventriculotomy; infundibulectomy; or patch reconstruction. The outflow tract after infundibulectomy may appear irregular and show areas of kypokinesia or akinesia. Occasionally, the outflow tract is adherent to the posterior aspect of the sternum. This area then appears immobile and fixed. Its recognition is important, since it could present technical difficulties at re-operation.

After patch reconstruction of the outflow tract, the patch may dilate and show various degrees of prominence. On occasion, aneurysm formation does occur. In the series of Hawe *et al.*[11] the incidence of aneurysm formation in the outflow tract in

cases with Ivalon patches was 33 per cent; 9 per cent in cases with teflon patches; and 8 per cent in those with autogenous pericardial tissue patches. Rosenthal *et al.*[20] reported an incidence of 7 per cent of outflow tract aneurysm (8 out of 135) in patients with pericardial outflow tract patches. The high incidence of aneurysm formation in outflow tract patches made with Ivalon and teflon has been noted by various groups. It is believed that a pericardial patch cut as small as possible prevents progressive dilatation of the patch leading to aneurysm formation.

Nine right ventricular aneurysms were found among 7 of 76 patients with postoperative angiocardiograms (13.8 per cent). Three of these occurred in the same patient: 2 simultaneously after the first surgical correction; and a third after a second correction which included a patch across the annulus. Three aneurysms occurred in patients with patches across the annulus and 6 in patients without patches. In contrast, most series report aneurysms in patients with outflow tract patches and relate the incidence of aneurysm formation to the type of material used and size of the patch. Our finding is probably related to the thoroughness and severity of the muscle resection. In each of our 6 cases the surgical note specified that a "thorough" muscle resection has been performed including "resection of cristal bands." Perhaps the infundibulectomy and ventriculotomy weakened the wall of the outflow tract changing its contraction pattern and leading to aneurysm formation. In each of these patients residual pulmonary valvular stenosis was shown by angiography; and the right ventricular pressures were 42, 42, 110, 148, and 76 mm. Hg, respectively. The residual pulmonary stenosis may have increased the tension in the right ventricular wall facilitating aneurysm formation. Hipona and Bloom[12] reviewed the problem of postoperative aneurysm of the right ventricular outflow tract and found the common denominator in all their patients to have been an infundibulectomy.

Three of our 4 cases with false aneurysm were in patients without outflow tract patches. Angiographically it is difficult to distinguish between a false and a true aneurysm in patients following correction of Tetralogy of Fallot. False aneurysms may have a short neck and irregular margins, while true aneurysms, particularly in cases with outflow tract patches, have wide necks and are smooth. In the series of Rosenthal *et al.*[20] the false aneurysms extended posteriorly and to the left, while the true aneurysms extended anterosuperiorly. In contrast, one of our false aneurysms extended posteriorly, another anterosuperiorly, and a third anterolaterally. Position is, therefore, not a reliable aid in differentiation of true from false aneurysms. The appearance of the margin of the aneurysm is not reliable either in distinguishing between these types of aneurysms, since the margin of the true aneurysm of the outflow tract after a patch may also appear quite irregular.

The severity of outflow stenosis, whether infundibular, valvular, or supravalvular, cannot be determined postoperatively by the angiographic appearance. The most common site for residual outflow tract obstruction was the valve and valve ring area.[10] Catheterization data are needed to determine the significance of an apparent area of stenosis demonstrated angiographically.[6]

SUMMARY

The pre- and postoperative chest roentgenograms and angiocardiograms were reviewed in 108 patients who had undergone complete surgical correction for Tetralogy of Fallot.

(1) Almost all postoperative chest roentgenograms showed increased cardiac size and increased prominence of the main pulmonary artery segment. The degree of postoperative cardiomegaly or outflow tract prominence could not be significantly correlated with peak right ventricular systolic

pressure, size of residual shunt or residual gradient across the right ventricular outflow tract.

(2) Postoperative residual anatomic abnormalities may be demonstrated angiocardiographically in both patients with clinically acceptable results and those with poor results. Among the most common are residual ventricular septal defects, irregularities at the site of the ventricular septal defect patch, hypokinesia or akinesia at the ventriculotomy site, adherence of the outflow tract to the sternum, dilatation of the outflow tract and main pulmonary artery after outflow tract reconstruction, or residual pulmonary valvular stenosis.

(3) Nine right ventricular aneurysms were found among 7 of 76 patients with postoperative angiocardiograms (13.8 per cent). Six of these were secondary to infundibulectomy and ventriculotomy. The right ventricular pressures were elevated in each. The diagnosis of postoperative aneurysm of the outflow tract requires cardiac catheterization and angiocardiography. Even after these are done, it is often difficult to differentiate between a true and a false postoperative outflow tract aneurysm.

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CHORIOANGIOMA OF THE PLACENTA*

A CAUSE OF CARDIOMEGALY AND HEART FAILURE IN THE NEWBORN

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CARDIOMEGALY and heart failure in the newborn may occasionally be caused by large arteriovenous shunts, usually arteriovenous malformations of the vein of Galen or vascular tumors of the liver.[10,14] Less common sites of shunting have been reported with cutaneous hemangiomas, pulmonary arteriovenous fistulae, communications between the subclavian artery and left innominate vein, and the left internal mammary artery and portal vein.[14]

Significant arteriovenous shunting may also occur in the extracorporeal part of the systemic circulation of the fetus. Large hemangiomas of the placenta (chorioangiomas) bypass the circulation of the villi and cause direct communication between the umbilical artery and vein. The location of such arteriovenous malformations creates a distinct syndrome characterized by hydramnios, fetal hypoxia and a high output state of the fetal heart.[4,13,15,17] These newborn infants may present with unexplained cardiomegaly and heart failure.[4,13] In most instances this condition is reversible, since delivery and severance of the cord is *per se* therapeutic.

Chorioangioma is the most common benign tumor of the placenta, and yet it is rarely encountered, because placental tumors are generally quite infrequent. It has received very little attention outside the obstetrical literature, despite its obvious significance for the pediatrician, neonatologist and pediatric radiologist.

We report 2 cases of placental chorioangioma associated with neonatal respiratory distress, cardiomegaly and heart failure. Both infants presented diagnostic problems until the significance of the placental tumors became evident.

REPORT OF CASES

CASE 1. A 4 hour old male infant was admitted to The Children's Mercy Hospital for respiratory distress and sclerema. He was born to a 36 year old gravida 2, para 2, VDRL negative mother, after approximately 38 weeks gestation. Pregnancy was complicated by a weight gain of 16.3 kg. and peripheral edema. Delivery was spontaneous after an 8 hour and 40 minute duration of labor. A large amount of amniotic fluid was thought to be present (hydramnios). The baby's weight was 2,183 gm. Apgar scores were 2 and 5 at 1 and 5 minutes, respectively, with cyanosis, tachycardia, tachypnea, subcostal and intercostal retractions and bilateral rales present at birth. A systolic murmur, Grade 2/6, was heard best along the left sternal border. There was sclerema of the buttocks and lower extremities, as well as generalized edema.

The patient was initially resuscitated with oxygen, then ventilated by respirator via nasotracheal tube. Upon admission the pH was 7.03, PaO_2 56, and $PaCO_2$ 51 mm. Hg while breathing 100 per cent oxygen. Hemoglobin was 9.4 gm. per 100 ml., total protein 3.1 gm. and albumin 1.95 gm. per 100 ml. Bilirubin was 1.8 mg. per cent, all indirect.

Roentgenographic examination of the chest revealed massive cardiomegaly with the cardiac silhouette occupying nearly the entire chest (Fig. 1*A*). The electrocardiogram showed biventricular hypertrophy as well as T wave changes.

On the second day of life the infant developed signs of disseminated intravascular coagulation (prolonged partial thromboplastin time, decreased plasma fibrinogen and platelets). He was treated with heparin and blood transfusions. Improvement was evident over the next few days, both regarding cardiorespiratory

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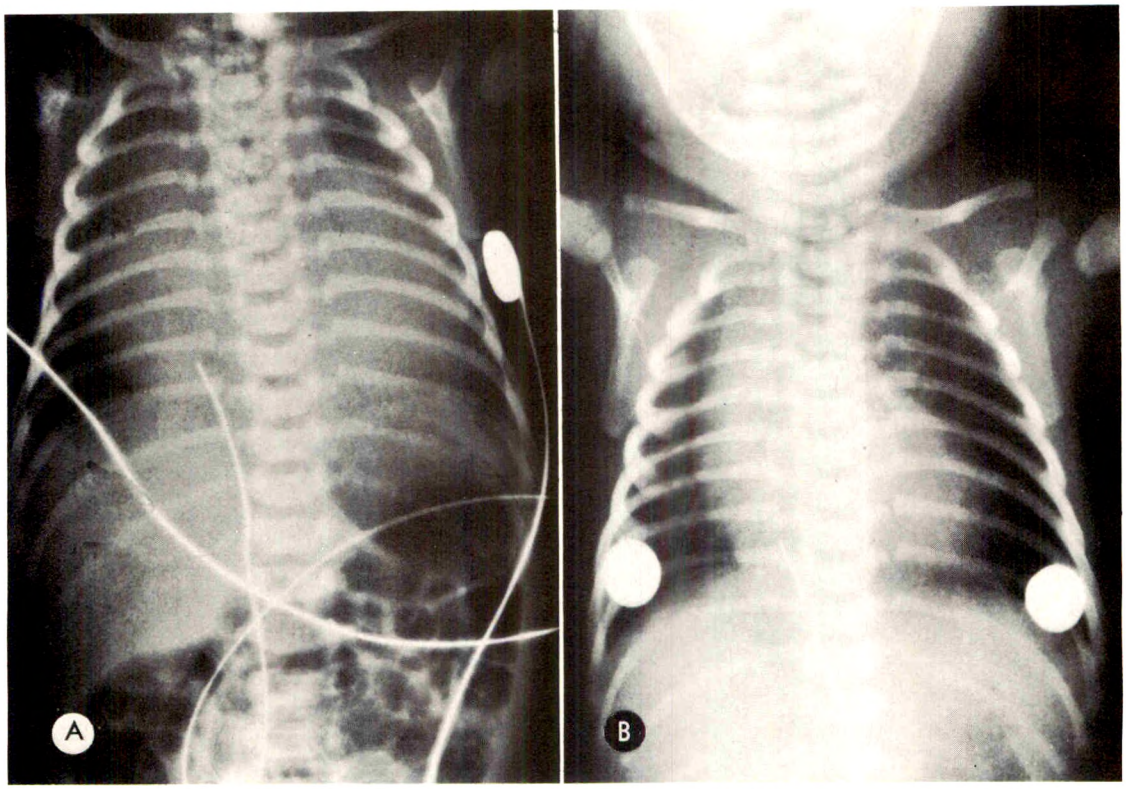

Fig. 1. Case I. (*A*) Marked cardiomegaly noted 6 hours after birth. The patient presented with clinical manifestations of hydrops fetalis. (*B*) Roentgenogram on the 10th day shows cardiac size almost within normal limits.

function and blood clotting. On the 5th hospital day the degree of cardiomegaly was less marked on roentgenograms, and there was improvement of the electrocardiographic findings. Over the same period of time, the patient's color was greatly improved, oxygen requirement decreased, heart rate became normal, and the heart murmur disappeared. Ventilatory assistance was discontinued and the patient was breathing room air on the 7th day. Subsequently, there was resolution of the sclerema and the clotting mechanism returned to normal. On the 10th hospital day heart size was within normal limits (Fig. 1*B*). A slow, steady recovery ensued and the patient was discharged at the age of 1 month.

The placenta weighed 500 gm. It was largely composed of multiple 1–4 cm. nodular areas distributed throughout the maternal and fetal aspect; some nodules were white, others dark red in color (Fig. 2*A*). On section, the nodules consisted of either red hemorrhagic tissue, or white, firm and glistening tissue. Microscopic examination showed multiple nodules of small capillary vessels arranged in lobules, with a small amount of fibrous connective tissue between the capillaries. (Fig. 2*B*). In some areas the capillaries were full of blood, in others they were bloodless or infarcted. Normal villi were not seen in these areas. Intervening placental villi, fetal membranes and umbilical cord were normal. The final anatomic diagnosis was multiple chorioangiomas of the placenta.

Case II. A female infant was born to a 37 year old, gravida 7, para 2, mother after approximately 32 weeks gestation. Pregnancy was complicated by marked abdominal distention, causing pain and respiratory distress. Fetal parts were not palpable. At approximately 30 weeks gestation amniocentesis was carried out twice, revealing marked hydramnios. A total of 3,000 ml. of clear amniotic fluid was removed.

The infant was delivered spontaneously after a 10 hour uneventful labor. Her weight was 1,927 gm. Apgar scores were 4 and 6 at 1 and 5

minutes. The infant was pale, limp and in obvious shock. She was resuscitated with oxygen delivered by bag and mask. An umbilical arterial catheter showed aortic blood pressure of 32 cm. of water. There was tachypnea and dyspnea. Breath sounds were poor with diffuse rales present bilaterally: pH was 7.35, $PaCO_2$ 35 and PaO_2 220 mm. Hg while breathing 100 per cent oxygen.

Roentgenograms of the chest showed cardiomegaly with essentially normal lung fields. The electrocardiogram was consistent with biventricular hypertrophy. Laboratory examinations revealed anemia (Hb 7 gm. per 100 ml.), hypoproteinemia and hypoalbuminemia.

The patient was treated with oxygen delivered by hood and 3 small transfusions of packed red cells. She improved markedly and on the 6th hospital day was placed in room air. Repeat roentgenographic examination of the chest revealed normal cardiac size. The patient was discharged at the age of 1 month.

The placenta measured 27×20×8 cm. and weighed 1,250 gm. A large circumscribed, firm, globular mass, 10 cm. in diameter, protruded from the fetal and maternal surface, in direct contact with the insertion of the umbilical cord. Sections showed a large hemorrhagic lobulated mass, extending throughout the depth of the placenta. The remainder of the organ was pale and anemic. Microscopic examination revealed multiple, thin walled vascular spaces, lined by a single layer of endothelium and a small amount of supporting connective tissue. There were areas of infarction and necrosis within the tumor. The diagnosis was chorioangioma of the placenta. This case has been the subject of a previous report.[15]

DISCUSSION

Hemangiomas arising from the chorionic tissue of the placenta are called chorioangiomas.[15,17] They are benign tumors consisting of dilated small vessels and capillaries, generally lined with a single layer of endothelial cells. These vascular structures are embedded in a groundwork of chorionic stromal cells.[12] The most common type of chorioangioma is the vascular type, mostly composed of vascular elements. Less common types are the relatively avascular embryonal form and the degenerative form with hyalinization.[6,12]

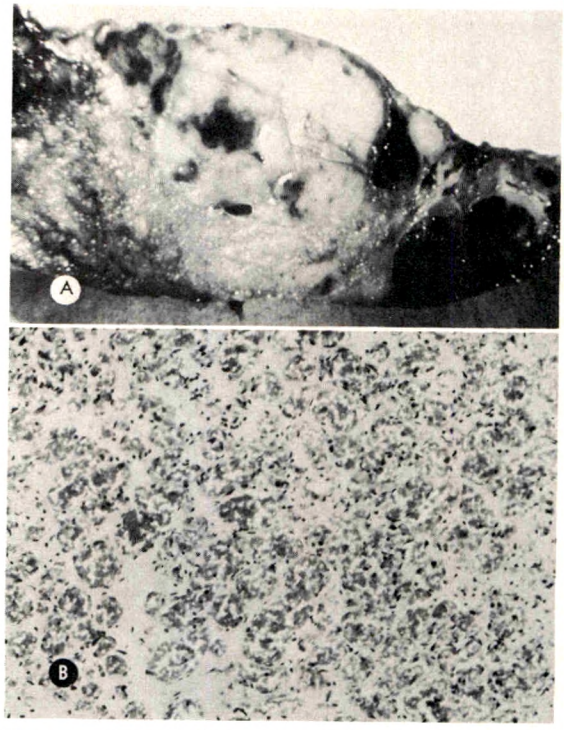

Fig. 2. Case 1. (*A*) Section of the placenta reveals multiple nodular tumors, some of them infarcted (white areas). (*B*) Microscopic examination shows a typical hemangioma, composed of a network of thin walled vessels filled with red cells in a loose connective tissue stroma (chorioangioma).

Chorioangiomas vary not only in the degree of vascularity, but also in size and relationship to the cord vessels. Such features determine whether a certain tumor will remain silent and clinically unsuspected, or cause severe gestational and perinatal complications.[7] Small tumors are usually discovered only upon careful sectioning of the placenta, whereas large ones are immediately evident on inspection (Fig. 2*A*). These variations have caused marked discordance in the reported incidence of chorioangioma. When all placentas are sectioned routinely, chorioangiomas are discovered as often as 1 per 77 deliveries.[18] When only the large symptomatic tumors have been taken into consideration, the reported incidence is as low as 1:9000.[9]

Large, vascular chorioangiomas function as arteriovenous malformations of the

fetal systemic circulation causing hypervolemia, cardiac dilatation, hypertrophy and ultimately heart failure in the fetus.[4,10,13,17] After delivery these infants may present clinical manifestations of congestive heart failure and roentgenographic evidence of significant cardiomegaly (Fig. 1*A*). Differential diagnosis includes congenital heart disease, neonatal cardiomyopathies[14] and cardiomegaly secondary to respiratory disease or persistence of the fetal circulation.[8] Arteriovenous malformations should also be considered in the differential diagnosis of neonatal cardiomegaly and heart failure, especially since early surgical closure of these shunts may be quite gratifying. A thorough search for such arteriovenous communications should be extended to include the placenta, a fact not adequately stressed in the literature. When a chorioangioma is discovered the nature of the cardiorespiratory signs and the associated cardiomegaly may be explained, and a favorable prognosis may be expected with appropriate therapy, in most instances within a few days.

Hydramnios is commonly present with large chorioangiomas.[4,5,15,18] The exact mechanism is not known, and a number of theories have been proposed for its explanation.[15] Hydramnios was present in both cases of this report and raised prenatal suspicion of central nervous system or gastrointestinal tract anomalies.[16] Chorioangioma should be included in the differential diagnosis of hydramnios.

Other complications of chorioangioma are prematurity (probably related to hydramnios)[17] and maternal toxemia.[7,17] Heart failure and hypoxemia may be the principal reason for the increased number of stillbirths and high perinatal mortality.[17] When shunting is significant, a low pressure system in the hemangioma is thought to deprive the functioning placental villi from adequate blood flow[13] with subsequent fetal hypoxia and retarded intrauterine growth.[12]

Since the placenta carries out the gas exchange function, it acts as a fetal lung. It was thus postulated that arteriovenous malformations of the placenta should combine the pathophysiologic derangements of both the systemic and pulmonary circulations.[13] Although polycythemia accompanies pulmonary arteriovenous shunts, this disorder has not been noted with chorioangiomas. In fact, in most instances the newborn presents with marked anemia,[11,15,17] as noted in our cases. Thrombocytopenia has also been described[7,17] and it is likely that both disorders are caused by the same mechanism operating in large systemic hemangiomas.[1] Disseminated intravascular coagulation in the second infant of this report may be coincidental. It is possible, however, that intravascular thrombosis occurred in the vascular spaces of the tumor leading to the syndrome of generalized defibrination and depletion of coagulation factors.[1]

Our 2 infants presented with hypoproteinema and hypoalbuminemia, as have other patients in previous reports.[2,11,15] This phenomenon has been attributed to sequestration of protein-rich fluid into the loose connective tissue of the angioma.[2]

Hemangiomas of the skin and other organs of the newborn infant have been described to occur more frequently in association with chorioangiomas.[5,9,17,18] If present, they may offer a clue to the possible existence of a placental vascular tumor. Cutaneous hemangiomas were not noted in our cases.

SUMMARY

Transient cardiomegaly and congestive heart failure associated with a clinical picture of hydrops fetalis were seen in 2 newborn infants.

In both instances the placenta harbored large hemangiomas (chorioangiomas), which have been described as functioning large arteriovenous fistulae.

It is almost certain that cardiomegaly under these circumstances is caused by systemic hypotension, increased vascular volume, and high output failure known to accompany other systemic arteriovenous shunts in the neonate, such as large cu-

taneous hemangiomas, hemangio-endotheliomas of the liver and arteriovenous aneurysm of the vein of Galen.

Because of their location, chorioangiomas are associated with a more complex clinical syndrome, which frequently includes hydramnios.

Chorioangiomas should be included in the differential diagnosis of neonatal cardiomegaly and maternal hydramnios.

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ABDOMINAL AORTIC ANEURYSM IN CHILDHOOD*

A NONINVASIVE APPROACH TO THE DIAGNOSIS

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ANEURYSMS of the abdominal aorta in childhood are extremely rare lesions. This is evidenced by the experience of Nebesar *et al.*[5] During a 5 year period, at a large children's hospital, they performed abdominal angiography in 131 patients and failed to encounter a single incidence of aneurysm.

The purpose of this paper is to present an unusual example of such a lesion and describe its roentgenographic, scintigraphic, sonographic and arteriographic manifestations.

REPORT OF A CASE

D.P. (DMC No. 04 1663), a 9 year old Black male, was transferred from Haiti to Downstate Medical Center because of the finding of an abdominal mass. The child had been well until the age of 4 years, when he was hospitalized for 3 weeks in Haiti for treatment of a severe febrile illness which necessitated intravenous antibiotics and oxygen therapy. Unfortunately, the old records from that hospitalization were unobtainable. Since that time, the patient had complained of intermittent pain in the right groin and thigh, which had increased in severity during the past few years. No significant history of abdominal trauma could be elicited. Physical examination revealed a palpable mass in the right epigastrium. No bruit was audible and the peripheral pulses were within normal limits.

Plain roentgenograms of the abdomen demonstrated a bilobed calcified mass in the region of the third lumbar vertebral body. An upper gastrointestinal series showed anterior displacement of the stomach and first and second portion of the duodenum (Fig. 1*A*). Lateral deviation of both upper ureters was evident on intravenous urography (Fig. 1*B*).

Sonography and radionuclide angiography were performed initially as a noninvasive ap-

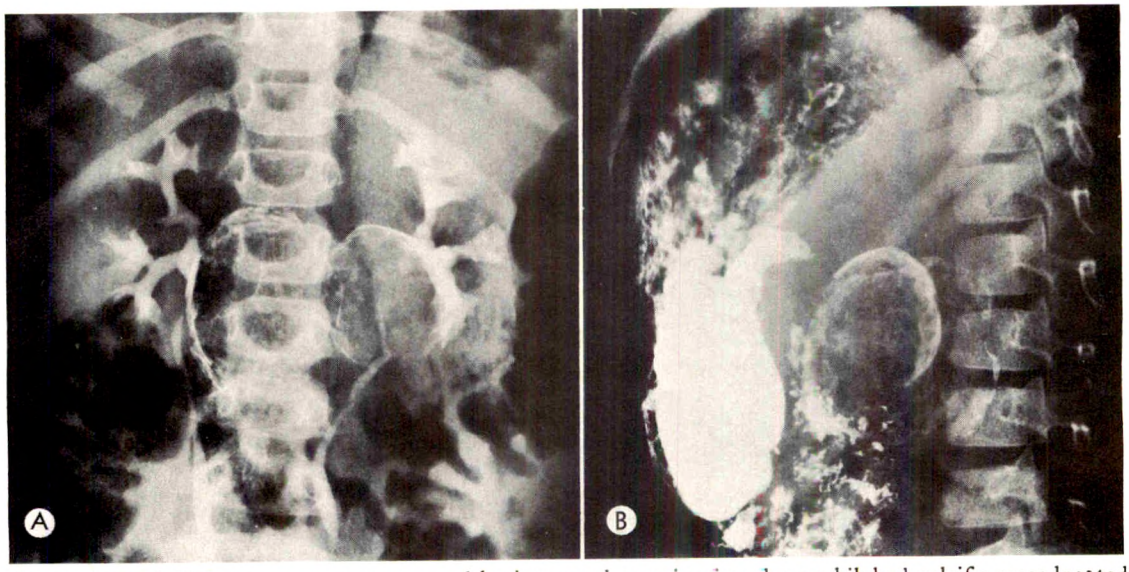

FIG. 1. (*A* and *B*) Intravenous urogram and barium meal examination show a bilobed calcific mass located in the midline and posteriorly. Both renal pelves and upper ureters are displaced laterally and compressed; the stomach and duodenum are pushed anteriorly.

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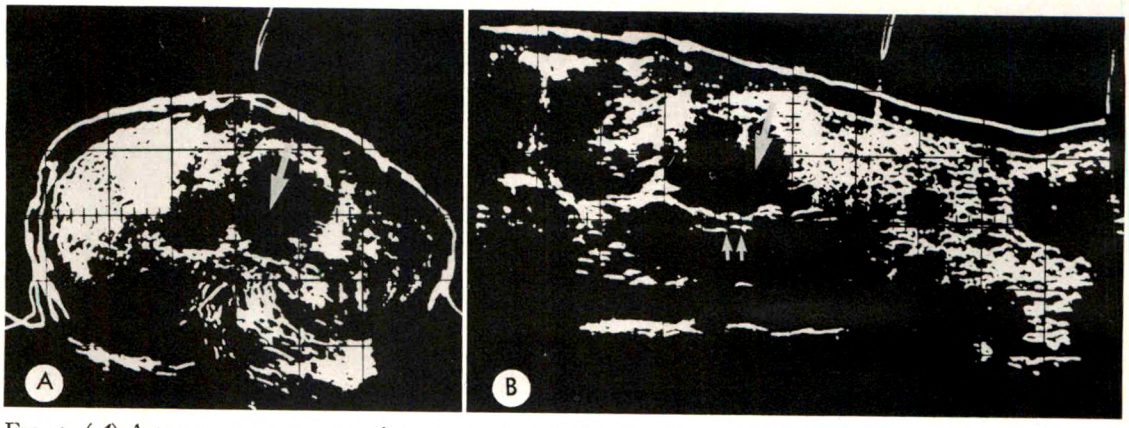

Fig. 2. (*A*) A transverse sonogram demonstrates a single echo-free mass which is bilobed (arrow). (*B*) The longitudinal sonogram shows compression of the abdominal aortic lumen (double arrow) and shows the mass (arrow).

proach to determine the organ of origin of the lesion.[1,3]

On serial transverse sonograms, there was a single, bilobed, essentially echo-free mass with an irregular wall-content interface (Fig. 2*A*). Longitudinal sonograms showed that the aortic lumen was compressed and its anterior margin could not be defined, suggesting that this mass was intimately related to the abdominal aorta (Fig. 2*B*). Rapid sequence serial scintiphotographs, with an Anger camera, after bolus intravenous injection of Tc^{99m} pertechnetate were then obtained. As aortic filling occurred, radioactive material could be seen accumulating in the region of the mass (Fig. 3*A*). Delayed exposures revealed persistent activity in the area

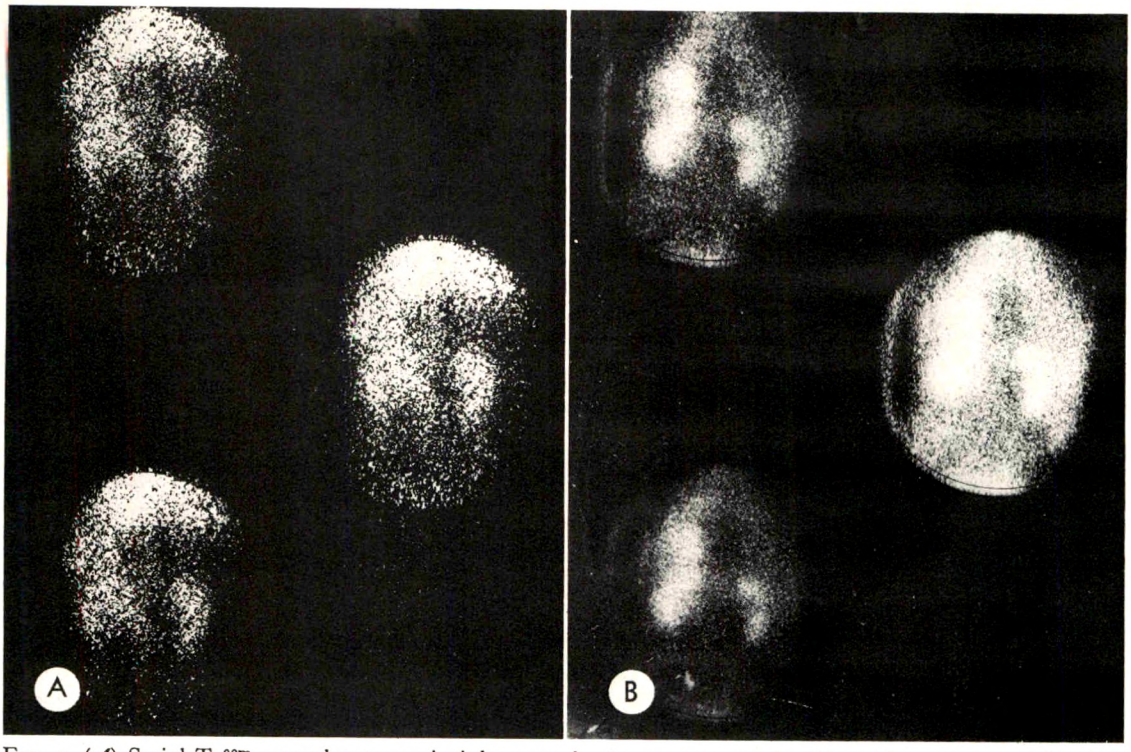

Fig. 3. (*A*) Serial Tc^{99m} pertechnetate scintiphotographs demonstrate early filling of an aneurysmal sac at 10–14 seconds after injection. (*B*) Exposure at 22–26 seconds reveals continued radioactivity in the aortic aneurysm after the remainder of the aorta has emptied.

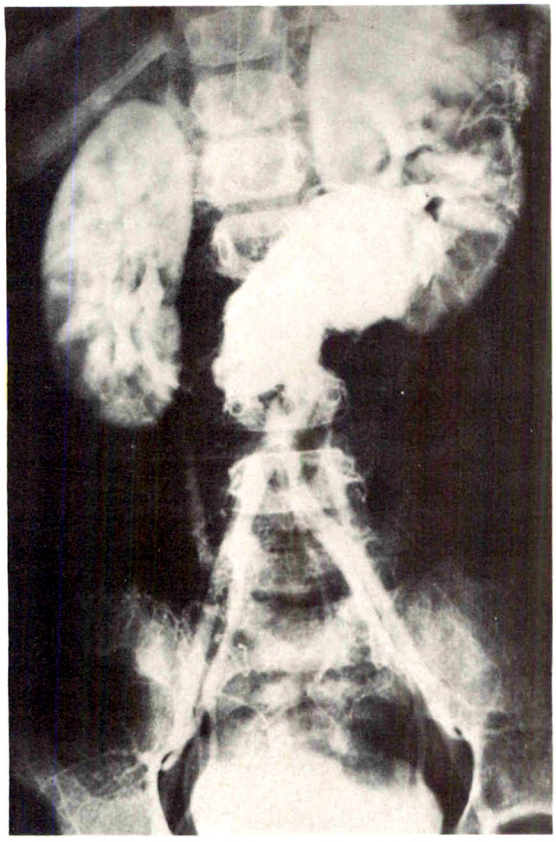

FIG. 4. Aortogram shows a large, bilobed, partly thrombosed aortic aneurysm. Distal flow is normal.

adjacent to the left renal hilum obliterating the medial border of the left kidney (Fig. 3*B*).

As a vascular origin of this mass had been strongly suggested by these studies, aortography was performed. The catheter was passed from the right axillary artery into the abdominal aorta. Injected contrast material demonstrated normal origins of the celiac, both renal, and superior mesenteric arteries. A large bilobed aneurysm containing considerable thrombosed material was present below the origin of the superior mesenteric artery. Runoff to the common iliacs was normal and there was no evidence of collateral circulation (Fig. 4).

At surgery, a large calcified bilobed aneurysm was found arising from the abdominal aorta, adherent to the left ureter and both renal arteries projecting posteriorly. The anterior wall was opened and numerous large clots removed. The aneurysm could not be resected in its entirety and the diseased segment was therefore bypassed. A 10 mm. De Bakey woven dacron interposition graft was sutured in place. The postoperative course of the patient was uneventful.

Pathologic examination of representative sections of the excised aorta showed the aortic wall to be thinned but intact. The adventitia and muscularis were normal. The elastica was somewhat degenerated and the vasa vasorum were surrounded by many lymphocytes and plasma cells. The intima contained multiple calcified atheromatous plaques. PAS and Gram stains were negative. The pathologic diagnosis was "aortitis of uncertain etiology." No organisms were cultured.

DISCUSSION

Aneurysms of any etiology are exceedingly rare in childhood, especially those of the abdominal aorta.[2,6] In this instance, there was no history of antecedent trauma and no clinical evidence of hyperlipidemia, periarteritis nodosa, Takayasu's disease, syphilis or degenerative or dysplastic disease of the arteries. There was, however, a history of prolonged febrile illness 5 years earlier, making it likely that this is a case of mycotic aneurysm.

The majority of mycotic aneurysms arise in the wall of already diseased aortas. However, primary mycotic aneurysms might be formed by bacterial infection through the vasa vasorum. Etiologic factors causing initial disturbance resulting in narrowing or obstruction of the vasa vasorum are many in the human body.[4] Healed mycotic aneurysms are generally asymptomatic except for pressure effects upon adjacent structures. Occasionally, they present catastrophically at the time of rupture. Lymphoplasmocytic infiltration in the wall of the aneurysm, although not diagnostic of an infective etiology, is strongly suggestive, especially in a young child.[7]

The differential diagnosis, which would be considered on plain film roentgenograms, upper gastrointestinal series and intravenous urogram, would include pseudocyst of the pancreas, calcified ganglioneuroma and an old intra-abdominal abscess or hematoma. Utilizing the combined noninvasive techniques of scintigraphy and sonography, the correct diagnosis was established almost categorically. Arteriography was confirmatory and served to rule out abnormalities of any other vessels in the area.

SUMMARY

A case of an abdominal aortic aneurysm in a 9 year old Black male is reported.

Abdominal roentgenograms, intravenous urograms and upper gastrointestinal series showed a bilobed calcified mass in the retroperitoneal space without defining the organ of origin.

This case illustrates the usefulness of noninvasive techniques such as sonography and radioisotope angiography in determining the vascular origin of an unusual mass in a child. The principal purpose of arteriography was to rule out unsuspected lesions in other arteries.

Although the pathologic findings were somewhat equivocal, the clinical information strongly suggested that this represented a mycotic aneurysm.

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PULMONARY FINDINGS IN GAUCHER'S DISEASE*

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GAUCHER'S disease is a relatively uncommon, but by no means rare, disease. Much has been written about it in the medical literature in which the full spectrum of manifestations are described, including frequent reference to changes in the lungs. The radiologic literature has stressed the classic bone changes, but only briefly described the lung changes. Interestingly, these limited references to pulmonary changes have dealt only with children.

The purpose of this paper is to call attention to the changes seen in the lungs and to report 3 patients, including, for the first time, an adult.

According to Fredrickson and Sloan[2] the underlying abnormality in Gaucher's disease is a defect in the enzyme B-glucosidase. The deficient activity of this enzyme leads to accumulation of glucosylceramide in reticuloendothelial cells which become altered in appearance, the so-called Gaucher cells. These accumulate in and enlarge the organs of the reticuloendothelial system, particularly, the liver, spleen, and deep lymph nodes. These cells also accumulate in the bones and lungs and alter both their structure and function.

There are at least 2 populations of Gaucher's patients and possibly 3 or more. All forms have in common hepatosplenomegaly, Gaucher cells in the marrow, and elevated serum acid phosphatase.

Type 1 (adult type) is characterized by an absence of central nervous system involvement. The onset may be in childhood and most have symptoms or signs before the age of 2. It is usually slowly progressive with major findings being hypersplenism, bone pain, and pathologic fractures. However, they may die early due to hemorrhage or poor response to minor illnesses.

Type 2 (acute neuronopathic) is characterized by the presence of neurologic signs which usually develop before 6 months of age. Once they appear, the course progresses fairly rapidly, ending in death, frequently before age 2, usually from anoxia and infection related to pulmonary involvement.

Type 3 (subacute neuronopathic, juvenile) also has central nervous system abnormalities and Gaucher cells in non-neurologic tissues. The onset and survival time is much more variable here and this may not be a homogeneous group.

REPORT OF CASES

Case 1. P.M. is a 46 year old white female first seen at UMMC in June of 1973. With the exception of frequent epistaxis, she had been in good health until 20 years prior to admission when she experienced polymenorrhea after the birth of her first child. Fifteen years prior to admission, her second pregnancy ended spontaneously in the first trimester and was followed by vaginal bleeding requiring transfusion. Four years later a low platelet count, chronic anemia, and splenomegaly led to a splenectomy which corrected the bleeding diathesis. Hepatomegaly was noted 10 years ago and bone pain occurred 2 years ago. Family history indicates 1 sister with Gaucher's disease, 4 sisters without, 2 brothers not tested, and 3 siblings who died in childhood.

The major problem recently has been edema, plethora, and congestive heart failure. Pulmonary function tests were consistent with restrictive lung disease, while cardiac catheterization suggested that the failure was due to pericardial restrictive disease. The chest roentgenogram revealed a bilateral diffuse interstitial nodular pattern and a right upper lobe nodule (Fig. 1, *A* and *B*). A pericardiectomy was performed and biopsies obtained from the right lower lobe

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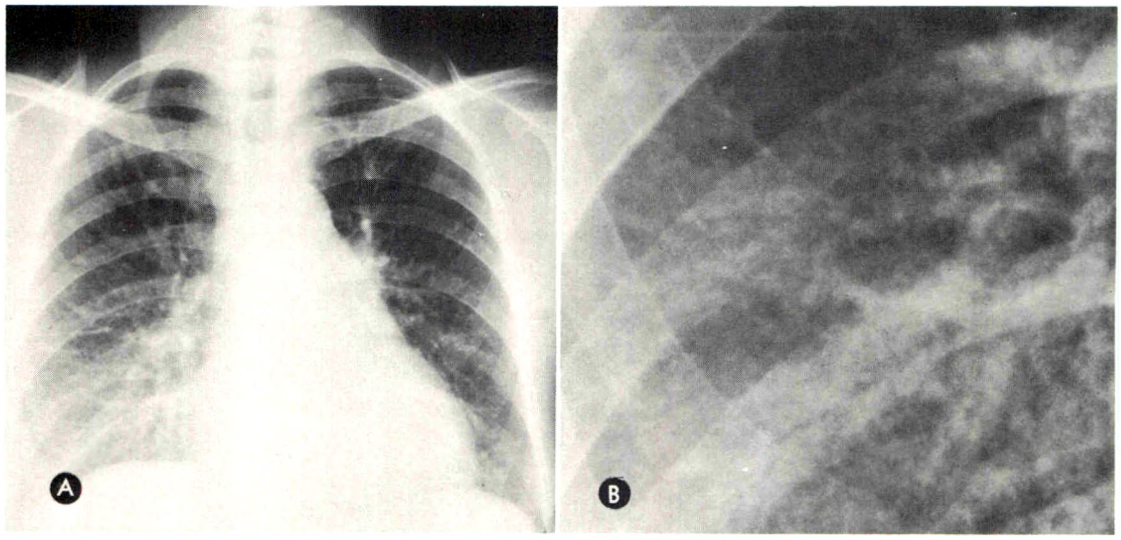


Fig. 1. (*A*) Chest roentgenogram reveals bilateral diffuse interstitial nodular pattern. (*B*) Detail from right lower lung field.

and from the right upper lobe nodule. The pulmonary parenchyma revealed Gaucher cells, but none were noted in the nodule which contained plasma cells, lymphocytes, and mast cells. In addition, amyloid was found in the walls of several vessels of the lung and in the walls of larger arteries and veins of the pericardium. The bone marrow also contained Gaucher cells.

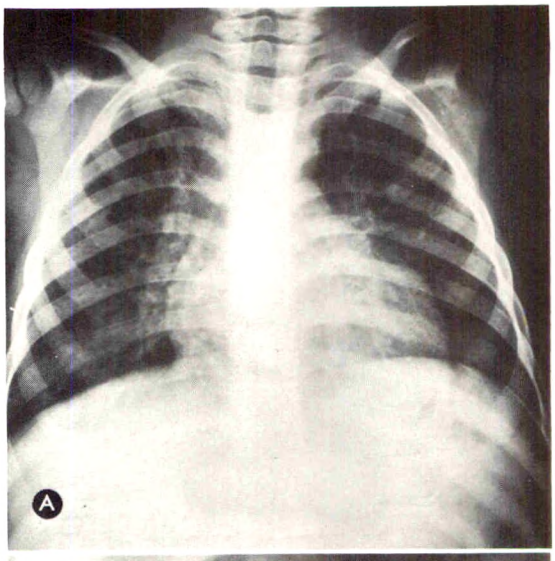
Case II. G.H. was first seen at UMMC in November, 1971 at the age of 3. The diagnosis of Gaucher's disease was made at 4 months when splenomegaly was discovered and a bone marrow revealed Gaucher cells. A splenectomy performed later confirmed the diagnosis. He has been hospitalized several times since birth for pneumonia, and at 3 years of age a chest roentgenogram revealed a reticular nodular pattern for the first time (Fig. 2, *A* and *B*). His chest roentgenogram was unchanged 7 months later (Fig. 3) and his condition is essentially stable, although he has developed left humeral head and bilateral femoral head necrosis.

Case III. B.H. is a sibling of G.H. (Case II) and was first seen at UMMC in June of 1972 at age 9 months. He had been hospitalized at 5 months for bright red painless rectal bleeding and hepatosplenomegaly. Gaucher's disease was suspected, but the bone marrow was negative. A bone marrow done at UMMC on June 26, 1972 was positive, and on September 25, 1972 the chest roentgenogram revealed an interstitial nodular pattern (Fig. 4).

DISCUSSION

We have observed 3 patients with Gaucher's disease who have similar abnormalities in their lungs. This prompted us to investigate this subject and we found rather conflicting reports in the literature. In the material by Fredrickson and Sloan[2] it is pointed out that Gaucher cells accumulate in, and alter the structure and function of, bones and lungs. However, the frequency of pulmonary involvement is not mentioned. In a recent text on pulmonary disease,[1] a paper is quoted in which the authors report a single case and indicate they could find no other reports of similar pulmonary involvement.[4] We have been able to find a total of 10 case reports[3–11] of patients with Gaucher's disease, in whom there was pulmonary involvement of one type or another. Not all of these had roentgenographic correlation.

In 1933 Merklen *et al.*[8] reported on a 51 year old man with Gaucher cells in the sputum. Myers[9] described an 8 year old female who died of Gaucher's disease who had Gaucher cells in the alveolar walls and



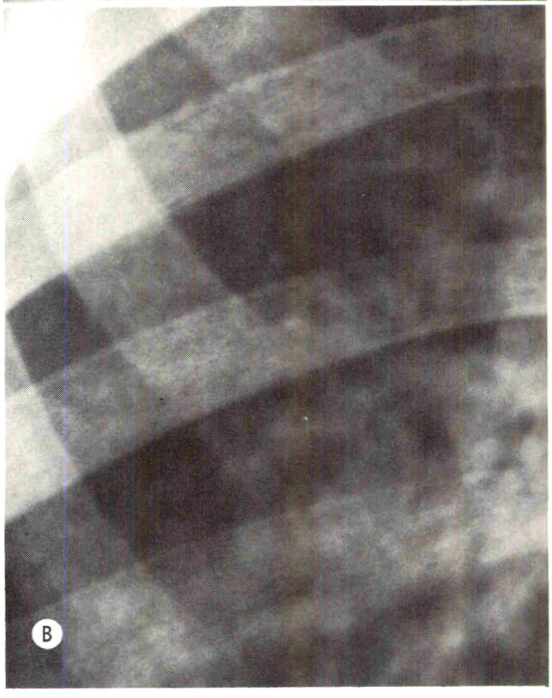


Fig. 2. (*A*) Chest roentgenogram reveals bilateral diffuse interstitial nodular pattern. (*B*) Detail from lower lung field.

sacs and in hilar and mediastinal lymph nodes. In 1950, a miliary pattern on the chest roentgenogram was described by Kauser.[5] Since that time there have been 6 other patients reported with nodular patterns in the lungs due to Gaucher's disease and these have generally been referred

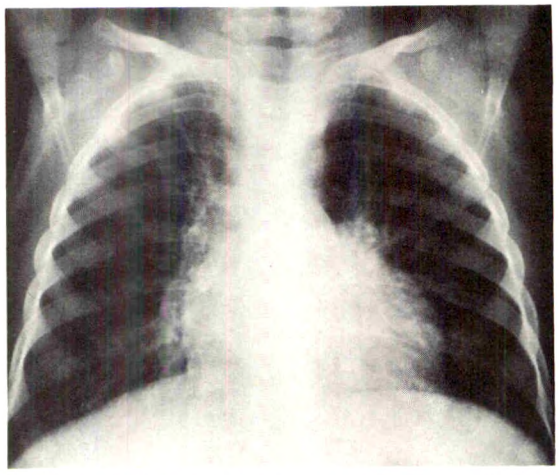


Fig. 3. Chest roentgenogram taken 7 months after 2*A* shows similar appearance.

to as miliary in appearance.[3,4,6,7,10] These were all children. One other type of pulmonary involvement reported was a case of severe pulmonary hypertension due to obstruction of the pulmonary capillaries by Gaucher cells.[11] This patient, an adult male, also had occasional Gaucher cells in the alveolar spaces but no mention is made of a nodular pattern on the chest roentgenogram.

While patients with Gaucher's disease do have an increased incidence of pulmonary infections,[2] the appearance of a nodular pattern diffusely throughout both lungs should raise the possibility of involvement by the primary process. While this finding

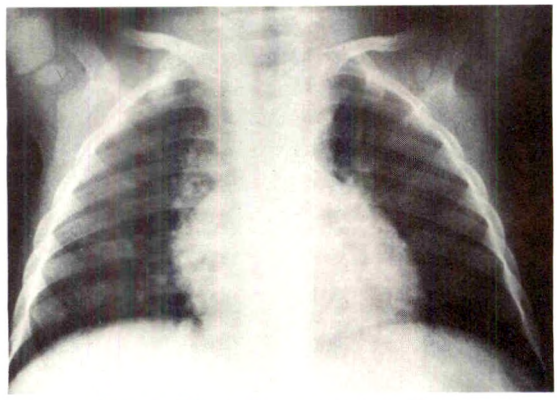


Fig. 4. Chest roentgenogram shows bilateral interstitial nodular change.

has previously been reported only in children, adults can apparently develop the same change. One report claims this to be more common in the acute neuronopathic form of the disease,[7] however, with the small number of cases in the literature this may not be a valid conclusion. The actual incidence of this roentgenographic abnormality in all forms of Gaucher's disease is also unclear for the same reason. Furthermore, it remains uncertain as to whether all who develop histologic evidence of involvement will ultimately have roentgenographic manifestations.

CONCLUSION

Gaucher's disease is an uncommon hereditary disorder which results in storage of glucosyl-ceramide in the cells of the reticuloendothelial system and other organs. The lungs are one of the organs affected, although the incidence remains unclear.

Our 3 patients confirm the small number of previous reports which indicated that the typical finding in the lungs is an interstitial nodular pattern, and for the first time this pattern has been observed to develop in an adult with this disease.

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I wish to thank Dr. William Martel for bringing Case 1 to my attention and for his encouragement in writing this paper.

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VALUE OF CHEST RADIOGRAPHY IN THE DIAGNOSIS OF POTTER'S SYNDROME AT BIRTH*

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BILATERAL agenesis or severe dysplasia of the kidneys is almost always associated with maternal oligohydramnios, since fetal urine contributes significantly to the formation of amniotic fluid.[1,2,6,7] These infants present at birth with certain features known as "Potter's syndrome." It consists of a typical facial appearance (hypertelorism, prominent epicanthic fold extending from the forehead to the cheeks, flattened nose, receding chin, low set ears containing little cartilage and an over-all impression of senility), as well as positional deformity of the legs and feet, renal and genital anomalies and bilateral pulmonary hypoplasia[1,6,12] (Fig. 1, *A* and *B*). They are usually born prematurely, most often by breech presentation, and tend to be small for gestational age if delivered beyond 34 weeks of gestation.[1] There is a male to female incidence ratio of approximately 3:1.[7]

Many infants with Potter's syndrome are stillborn. The majority live only a few hours after birth, although some infants with lesser degrees of pulmonary hypoplasia may survive for several days.[12] The cause of early death is bilateral pulmonary hypoplasia, complicated by early manifestations of the "air-block syndrome."[10,12] The hypoplastic lungs of these infants are unable to tolerate the negative intrapleural pressures created by the respiratory muscles in expanding the bony thorax. Alveolar rupture follows and air leaks into the pulmonary interstitium, mediastinum and pleural spaces. Efforts to resuscitate and ventilate these infants also contribute to the air-block syndrome.

It has been postulated that most of the anatomic abnormalities of Potter's syndrome, including pulmonary hypoplasia, are caused by lack of fetal urine with subsequent oligohydramnios and uterine compression of the fetus.[2,13] There is, however, no unanimous agreement on this point, as there are some inconsistencies between volume of amniotic fluid and lung development.[5,8,9]

Recently several cases with clinical features of Potter's syndrome were described, but without renal dysfunction. Oligohydramnios from other causes has been universally present however.[13] It was, therefore, suggested that the term "Potter's syndrome" be replaced by the term "oligohydramnios tetrad."[13] This description may be more accurate, although such cases are quite rare and constitute a small proportion of infants with the clinical syndrome.

The clinical features of Potter's syndrome are usually sufficient to establish the diagnosis. The clinical presentation, however, may be incomplete.[12] Twenty per cent of the cases described by Bain and Scott[1] lacked characteristic facial changes for the diagnosis to be made ante mortem. In such cases, "unexplained" air-block syndrome, such as pneumomediastinum and pneumothorax, should alert the physician to the presence of bilateral pulmonary hypoplasia, most likely caused by marked impairment of renal function *in utero*.[10,12] Since most newborn infants in respiratory distress receive some type of resuscitation, it is often difficult to establish that pneumomediastinum or pneumothorax is "unexplained." The diagnosis of bilateral agenesis or severe dysplasia of the kidneys may thus be missed, and unjustified heroic efforts may be initiated to prolong the life of these infants. Moreover, a lack of effort

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may occur when the diagnosis of renal agenesis is assumed on the basis of the clinical manifestations leading to the demise of an infant with normal kidneys. It is, therefore, extremely important that the diagnosis of bilateral pulmonary hypoplasia be established ante mortem as soon as possible, so that clinical aspects of the syndrome may be carefully sought for, and a study of the urinary tract be undertaken as soon as possible.

We have been impressed by a more or less distinct roentgenographic configuration of the neonatal chest whenever air-block syndrome results from bilateral pulmonary hypoplasia. Thus, oligohydramnios and probably renal non-function may be suggested from roentgenograms of the chest.

The purpose of this report is to describe the appearance of the chest roentgenogram in cases of pulmonary hypoplasia associated with Potter's syndrome or maternal oligohydramnios. Our experience is based on 7 newborn infants with "Potter's syndrome."

MATERIAL AND METHOD

In the 3 year period from 1972 through 1974, 6 infants with absent renal function and clinical manifestation of Potter's syndrome were admitted to The Children's Mercy Hospital in the first day of life. Five of these had bilateral pulmonary hypoplasia and died within 24 to 48 hours after birth. One infant had normal lungs and survived for 13 days. Necropsy revealed bilateral renal agenesis in 2, and bilateral severe dysplasia in 4. A seventh infant had the clinical features of Potter's syndrome, including pulmonary hypoplasia. This patient, however, proved to have normal kidneys at autopsy (Table 1).

All infants had anteroposterior and right lateral roentgenograms of the chest, obtained within 24 hours after birth. A standard technique was used. Films were exposed with a portable radiographic unit, at a 100 cm. focus-film distance, at 60–70 kvp., 1.6 mas. The beam was centered midway between the nipples for the anteroposterior view, and at the midthorax at the lower end of the scapula for the lateral view.

Fig. 1. (*A*) Typical facies of Potter's syndrome (Case 2). Note epicanthal fold, depressed flattened nose and receding chin. Ears are floppy and low set. (*B*) Same case. At autopsy no kidneys were found. Note the large oval shaped adrenals occupying the renal bed in the retroperitoneal space.

Roentgenograms were examined to as-

TABLE I

CLINICAL AND PATHOLOGIC FINDINGS IN 7 INFANTS WITH "POTTER'S SYNDROME"

Case	Sex	Prematurity	Intra-Uterine Growth Retardation	"Potter's Facies"	Deficient Ear Cartilage	Dry, Loose Skin	Genitourinary Anomalies	Lung Development[11]	Other Anomalies
1	M	+	+	+	+	+	Bilateral renal agenesis Absent ureters Hypoplastic bladder	Combined lung Wt. 9.5 gm. (Normal: 47 ± 17 gm.)	PDA Bowed legs Bilateral club foot
2	F	+	−	+	+	+	Bilateral renal agenesis Absent ureters Hypoplastic bladder Hypoplastic uterus	Lungs very hypoplastic	Congenital heart disease (PDA, pulmonary atresia, VSD)
3	F	+	+	+	+	+	Severe bilateral renal dysplasia R. ureter patent; L. atretic Imperforate hymen Hydrocolpos	Lungs small, filling 1/2 of pleural spaces	PDA Equinovarus feet Cerebral hypoplasia
4	M	+	+	+	−	+	Bilateral renal dysplasia Ureteral atresia Bladder hypoplasia Undescended testes	Combined lung Wt. 17 gm. (Normal: 29 ± 12 gm.)	Congenitally short bowel
5	M	+	−	+	−	−	Bilateral cystic renal dysplasia Ureteral atresia Hypoplastic bladder Microphalus Hypospadias, undescended testes	Combined lung Wt. 27 gm. (Normal: 47 ± 17 gm.)	PDA Imperforate anus with Recto-urethral fistula Bowed legs Equinovarus feet
6	M	−	+	+	+	+	Bilateral renal dysplasia Ureteral atresia Urethral atresia	Combined lung Wt. 75 gm. (Normal: 56 ± 25 gm.)	Bowed legs Equinovarus feet Choanal atresia? Scoliosis
7	M	+	−	+	+	+	Normal genitourinary tract	Combined lung Wt. 25 gm. (Normal: 39 ± 14 gm.)	PDA, Spade-like hands Equinovarus feet

sess thoracic and pulmonary volume. Early attempts to establish measurements for objective evaluation of the above volumes were abandoned. Such measurements would not be accurate and meaningful because of asynchronous exposure between anteroposterior and lateral views, variation of level of inspiration, and difficulty in establishing exact points for measurements. It was decided to examine roentgenograms on a clinical basis, *i.e.*, an over-all assessment by subjective impression. We believe this to be an acceptable method of roentgen examination. In most instances the roentgenographic diagnosis of "Potter's syndrome" was actually made in this manner and without previous knowledge of the clinical or pathologic diagnosis.

RESULTS

The clinical and pathologic features of 6 infants without renal function are presented on Table I.

The "air-block syndrome" was present in all 6 infants with renal nonfunction (Potter's syndrome). One baby had normal thoracic and lung volume on roentgenograms and normal lung development on postmortem examination (Case 6). Pneumomediastinum was noted in 5 infants and pneumothorax in 3 (2 left, 1 right). There were no roentgenographic features of tension pneumothorax or detectable evidence of pulmonary interstitial emphysema. In 5 cases (Table I) the thorax appeared small relative to the rest of the trunk and the lungs were small without recognizable structure, despite absence of compression by extrapulmonary air collections. In these cases the ribs followed a downward course and the diaphragm was high (at the level of between the sixth and eighth posterior

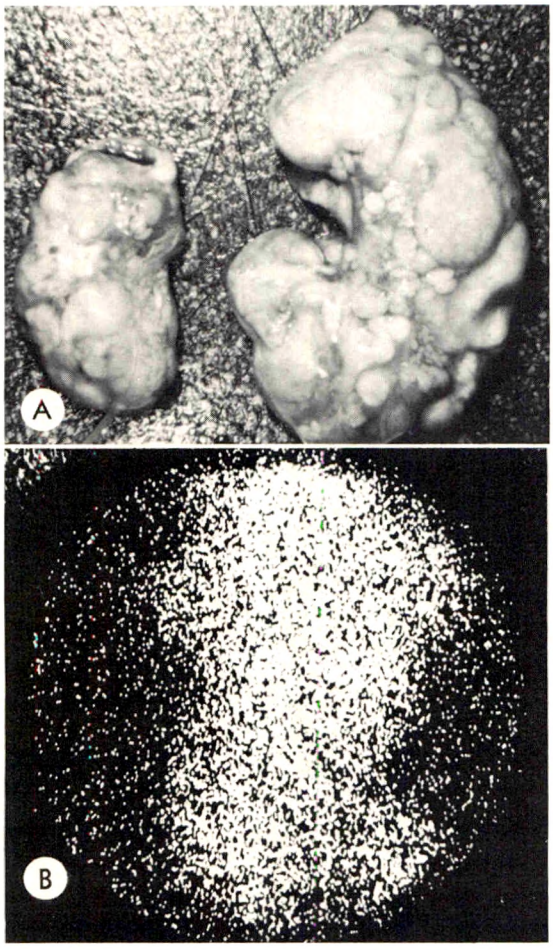

Fig. 2. Case 6. (*A* and *B*) Infant with the clinical features of Potter's syndrome, but without pulmonary hypoplasia. He survived 13 days. At autopsy there were severe bilateral cystic dysplasia of the kidneys (*A*) and bilateral ureteral atresia. An excretory urogram showed no visualization. A technetium 99m DTPA renal scan showed no evidence of renal uptake (*B*).

rib interspace). It was evident that the air-block was "*ex vacuo*." In the lateral view the anteroposterior dimension of the thorax was almost equal to the vertical diameter because of the high position of the diaphragm (Fig. 2–5). None of these features were noted in the infant who had normal lungs (Case 6). Absence of renal function in this instance was established ante mortem by the identification of Potter's facies, which led to excretory urography and a renal scan with technetium DTPA 99m (Fig. 2*B*).

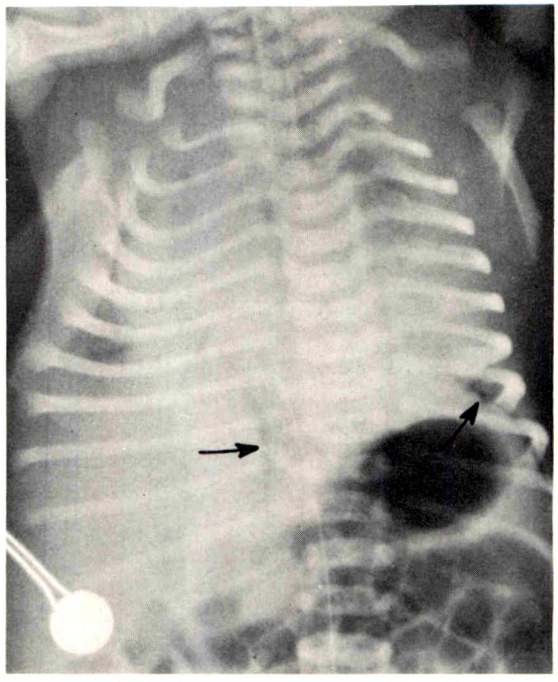

Fig. 3. Case 2. Severe bilateral pulmonary hypoplasia. Small pneumomediastinum seen along the left subpleural space and along the posterior mediastinum (arrows); it was more evident on lateral view of the retrosternal space. Small chest, almost entirely occupied by the mediastinal structures. Lungs barely visible, poorly aerated. Renal agenesis and pulmonary hypoplasia confirmed at autopsy.

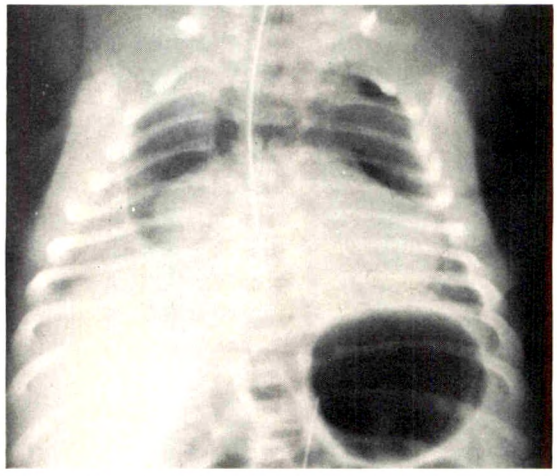

Fig. 4. Case 3. Bilateral pulmonary hypoplasia confirmed at autopsy. Downward course of ribs and small thoracic cage. Poorly aerated small lungs. Large pneumomediastinum.

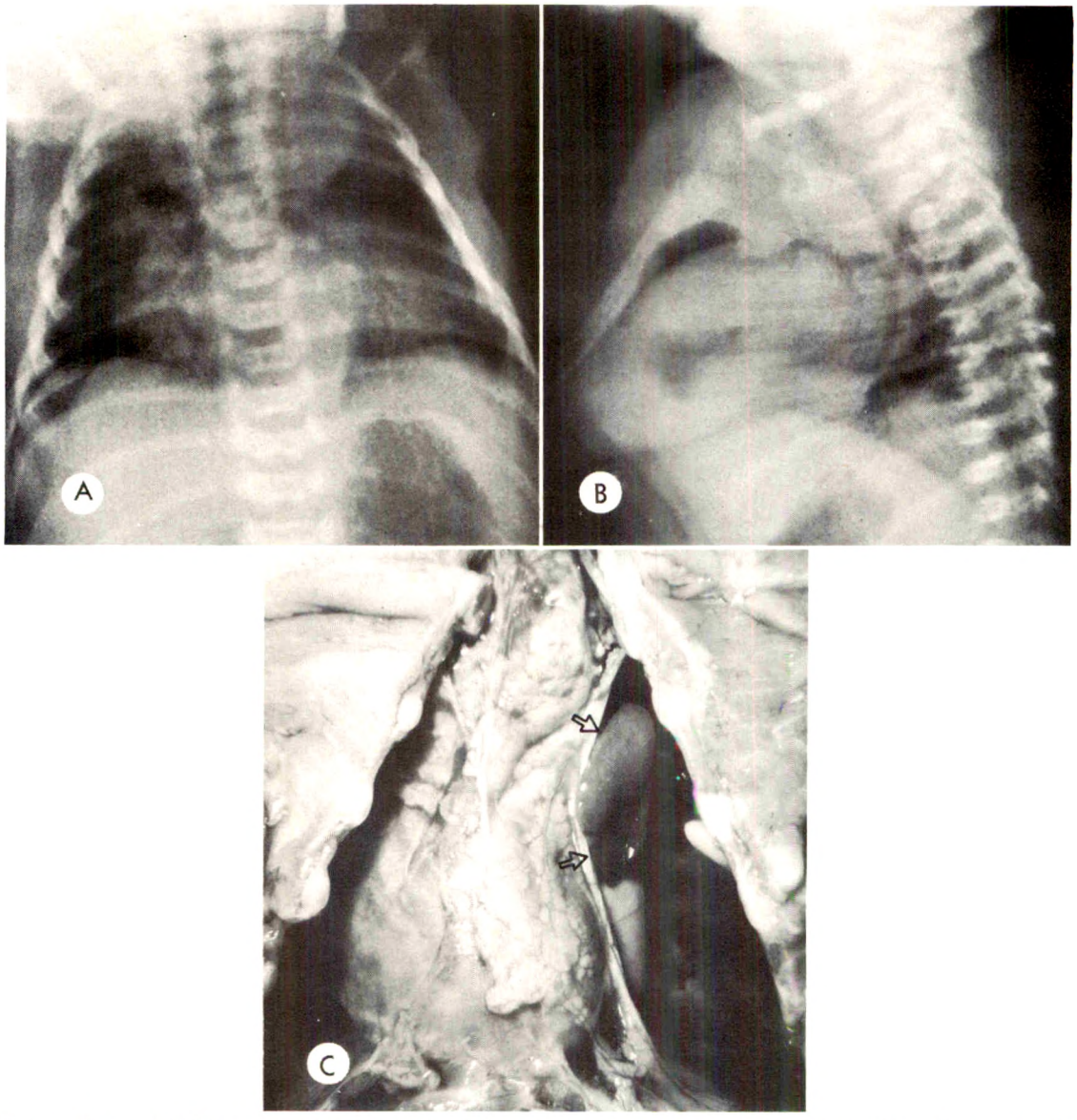

Fig. 5. Case 1. (*A*) Bilateral pulmonary hypoplasia and extensive pneumomediastinum. Thoracic cage small, mostly occupied by the heart and thymus. Air lucency bilaterally represents extrapulmonary air. (*B*) Lateral roentgenogram showing the chest completely occupied by the heart and mediastinum. (*C*) At postmortem examination very small hypoplastic lungs were found (arrows).

One infant with bilateral pulmonary hypoplasia, most likely caused by oligohydramnios secondary to chronic leakage of amniotic fluid, also presented roentgenographic findings of hypoplastic lungs and small chest (Case 7). He survived only a few hours. Autopsy revealed pulmonary hypoplasia but normal kidneys. This case may be more appropriately considered to represent an example of the oligohydramnios-tetrad syndrome.[13]

A schematic representation of the different features of the chest roentgenogram in bilateral pulmonary hypoplasia, as well as in the air-block syndrome without pulmonary hypoplasia is shown in Figure 6. Our experience indicates that infants with pneumomediastinum and/or pneumothorax

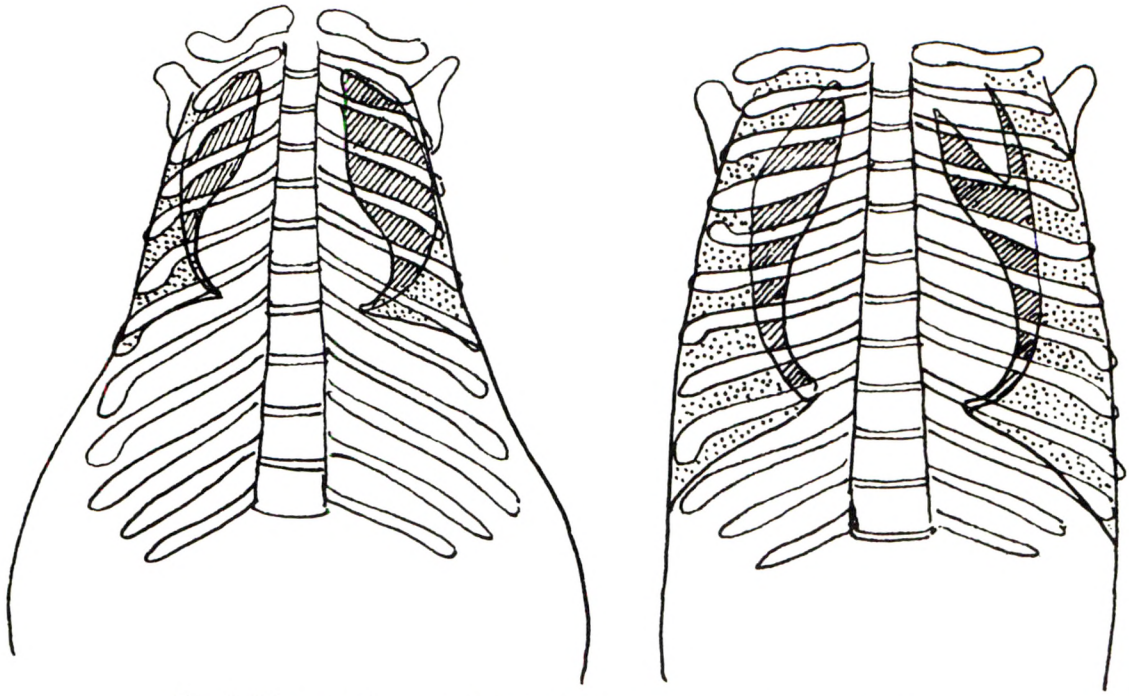

Fig. 6. Schematic drawing of the typical roentgen appearance of the chest with hypoplastic lungs (left) and normally developed lungs (right).

and normal lung development have the roentgen appearance of Figure 6, right. There is adequate thoracic volume, horizontal position of the ribs and well developed lungs (Fig. 7, *A* and *B*).

DISCUSSION

Pneumomediastinum, with or without pneumothorax, is almost always present in infants with bilateral pulmonary hypoplasia at the time of the first roentgenographic examination.[12] This fact was confirmed in our series of patients with Potter's syndrome. In no instance, however, was there roentgen evidence of pulmonary interstitial emphysema or pneumothorax under tension. If manifestations of the air-block syndrome are unexplained by such entities as meconium aspiration or mechanical ventilation, one should consider the possibility of Potter's syndrome or obstructive urinary tract anomaly resulting in diminished excretion of fetal urine.[10] In most instances Potter's syndrome will be confirmed by inspection of the infant. Occasionally, however, features may not be quite typical or immediately recognized.[1,12] Roentgenographic diagnosis of bilateral pulmonary hypoplasia as the cause of pneumomediastinum or pneumothorax will identify one of the cardinal features of Potter's syndrome. Similar changes on chest roentgenograms are noted in patients with bilateral pulmonary hypoplasia caused by oligohydramnios but without renal anomaly (Case 7). Because of the uncertainties in the diagnosis of renal agenesis or dysplasia, one should proceed immediately with roentgenographic, radioisotope, and laboratory investigations of the urinary tract. Indeed, our infant with the oligohydramnios tetrad was not treated vigorously, being assumed to have no kidneys. Autopsy disclosed a normal urinary tract (Case 7).

Low thoracic and pulmonary volume may also be caused by other entities such as severe asphyxia, central nervous system depression or skeletal dysplasia.[4] There may be areas of lobar atelectasis in these cases, and the presence of pneumomediastinum and pneumothorax depends on vigorous resuscitation. Differential diag-

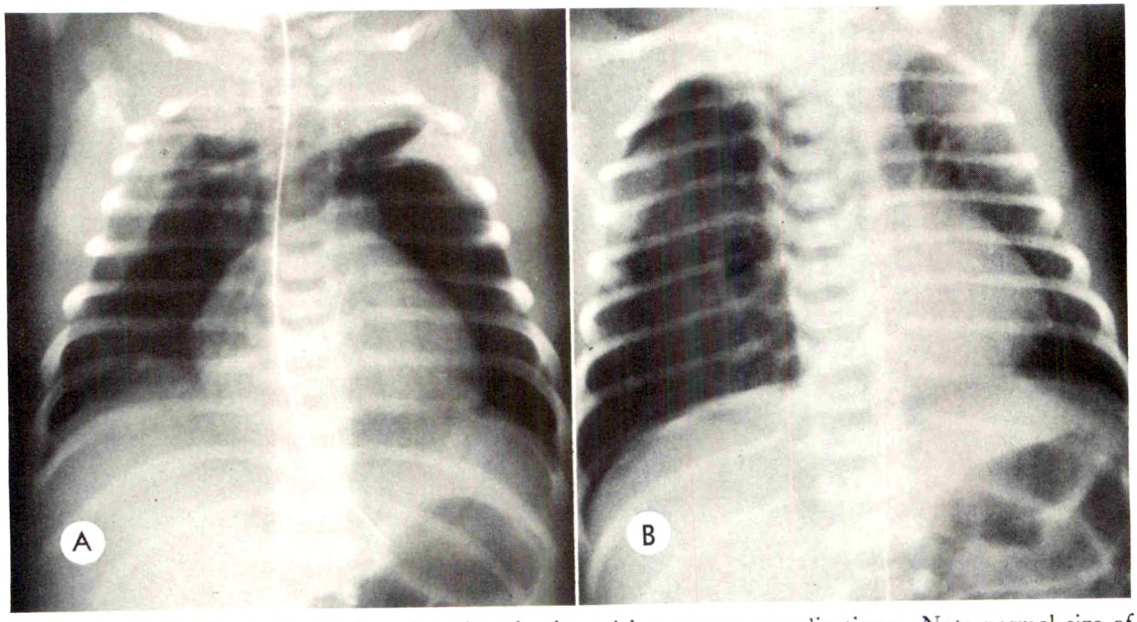

Fig. 7. (*A*) Full term infant with perinatal asphyxia and large pneumomediastinum. Note normal size of thorax and bilaterally well developed lungs albeit that lung structure is obscured by extrapulmonary air collection. (*B*) Premature infant with IRDS treated with CPAP. Note well expanded lungs, filling a normal thoracic cage. Horizontal ribs, low diaphragms. There is a right pneumothorax and a small pneumomediastinum.

nosis from Potter's syndrome should be based on the perinatal history (oligohydramnios) and obviously on the search for the facial and limb anomalies of the latter. Pulmonary hypoplasia related to skeletal dysplasia[3] or diaphragmatic hernia is easily recognizable on the roentgenograms.

Our Patient 7 is of great interest in that he had no pulmonary hypoplasia, despite lack of renal function *in utero*. Unfortunately, the history regarding the amount of amniotic fluid is incomplete. Breech presentation, Potter's facies, limb deformities, and pathologic findings suggest oligohydramnios. If so, then one may question the absolute dependence of lung development on the amount of amniotic fluid.

CONCLUSION

The present series of patients with pulmonary hypoplasia is small, since the disease is relatively uncommon. Our findings will have to be confirmed on a larger series, and there are rare exceptions to the rule.

We feel, however, that there is enough evidence from our patient material, as well as from observations of published roentgenograms,[10,12] to warrant the conclusion that pneumomediastinum and/or pneumothorax in the newborn, associated with decreased thoracic volume and poorly expanded and "structureless" lungs, should be viewed with suspicion of renal nonfunction and/or maternal oligohydramnios.

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HIATAL HERNIA AND GASTROESOPHAGEAL REFLUX IN INFANCY AND CHILDHOOD*

ANALYSIS OF THE RADIOLOGIC FINDINGS

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HIATAL hernia occurring in children has been recognized as a significant problem primarily in the past 2 decades with only 93 cases reported in the literature prior to 1951.[9] Since that time, pediatric centers in Europe, the United Kingdom, Toronto (Canada), Washington, D.C., and Stanford (California) have reported many patients with this condition treated both medically and/or surgically (Table I).[2,3,6,18,19,24,29,31] In striking contrast, the number of patients reported by the majority of pediatric centers in the United States have been few in number.[17,20,22,25,27,32]

The lower prevalence rate in North America (Toronto, Washington, D.C., and Stanford excluded) has never been completely explained. Guttman[21] has recently suggested that the traditional prone resting position of the North American infant (as contrasted to the usual supine position of the European baby) is a significant factor producing this difference. This factor could account for the lower incidence of patients with symptomatic hiatal hernia, but still fails to explain the large number of cases reported from Toronto and the infrequent roentgenologic demonstration of a hiatal hernia or reflux in pediatric patients presenting with the clinical symptoms of vomiting, dysphagia, failure to grow, gastrointestinal bleeding, anemia or substernal or epigastric pain.

In order to evaluate this discrepancy from a diagnostic viewpoint, the technique of roentgenologic examination and criteria of diagnosis used at the Hospital for Sick Children, London, England,[34] was studied and a similar approach was adopted at the Boston Floating Hospital for Infants and

TABLE I

REPORTED CASES OF HIATUS HERNIA

Source	Reporting Period (years)	No. of Cases	
		Medical	Surgical
Frenchay Hospital, Bristol, 1967[31]	17	—	114
Hospital for Sick Children, London, 1969[6]	24	723	164
Alder Hay Children's Hospital, Liverpool, 1955[18]	3½	5	30
Children's Hospital, Bremen, 1965[3]	10	—	226
Children's Hospital, Berne, 1969[2]	7	—	112
Hospital for Sick Children, Toronto, 1971[29]	15	—	80
Children's Hospital, Washington, D.C., 1968[24]	9	33	19
Babies' Hospital, New York City, 1965[22]	20	16	18
Children's Medical Center, Boston, 1964[17]	14	15	15
Children's Hospital, Dallas, 1969[25]	8	12	18
Children's Hospital, Los Angeles, 1965[32]	10	8	—
Ste. Justine Hospital, Montreal, 1971[20]	8	2	5
Children's Hospital, St. Louis, 1963[27]	25	3	8
Stanford University Hospital, Stanford, 1974[19]	1	13	4

* From the Department of Radiology, Boston Floating Hospital for Infants and Children (New England Medical Center Hospital) and Tufts University School of Medicine, Boston, Massachusetts.

Children. All roentgenologic examinations of the esophagus and upper gastrointestinal tract with this revised system from July, 1971 through March, 1973 were then reviewed. Out of a total of 285 infants and children examined, hiatal hernia and/or gastroesophageal reflux was demonstrated in 83 patients.

All patients with positive roentgenologic examinations were then analyzed from the clinical and roentgenologic aspect for an answer to the following questions: (1) from the aspect of diagnosis and treatment of the patient, what importance does the roentgenologic demonstration of hiatal hernia and/or reflux have in the clinical management of the patient; and (2) what relationship, if any, do the roentgenologic manifestations have to the symptomatology of the patient?

The clinical investigation (reported separately)[16] showed that roentgenologic demonstration of a hiatal hernia and/or reflux is of definite importance in the clinical management of the symptomatic child.

The purpose of the present paper is: (1) to describe the normal anatomy and physiology of the gastroesophageal region in infants and children and those alterations which have been found in patients who have a congenital hiatal hernia (with and without gastroesophageal reflux); (2) to present a technique of demonstrating hiatal hernia and/or gastroesophageal reflux in the pediatric patient; (3) to describe and illustrate roentgenologic signs of hiatal hernia and/or gastroesophageal reflux; and (4) to study the relationship between roentgenologic findings and the presence or absence of relevant clinical symptoms in a patient.

ANATOMIC AND PHYSIOLOGIC CONSIDERATIONS

Botha[4] removed the diaphragm, lower esophagus, upper stomach, and surrounding tissues *en bloc* from 115 children aged 32 weeks to 8 years (the majority ranged from newborn to 1 month of age). Dissection of these specimens (Fig. 1) revealed

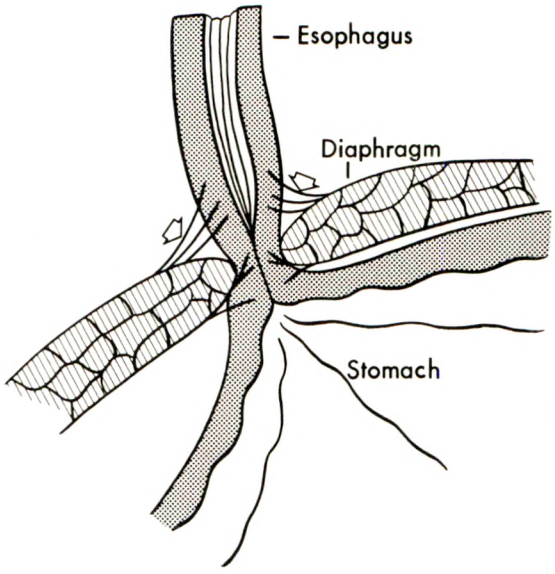

FIG. 1. The gastroesophageal region of the normal infant diagrammatically represented according to the anatomic dissections of Botha. The diaphragmatic sling forms a tunnel (3–8 mm. long) around the distal esophagus; the narrowed portion of the esophagus represents the physiologic lower esophageal sphincter; fibers forming the phrenoesophageal membrane (arrows) arise from the thoracic and abdominal surfaces of the diaphragm to insert into the muscular layer of the cardia and distal esophagus.

that, in the infant, the esophageal hiatus was not a simple opening in the diaphragm but consisted of a firm tunnel measuring 3-8 mm. in length. The esophagus was securely fixed to the diaphragm by a well-developed phrenoesophageal membrane (not a ligament) and the abdominal esophagus was so short as to be non-existent. At the level of the esophageal hiatus, the esophagus presented a constricted portion due to the tightly fitting diaphragmatic crura and the lower esophageal sphincter (L.E.S.). In the opened specimen, the point of transition between esophageal and gastric mucosal folds was located at the cardia in all of the specimens. (The epithelial transition was much more variable—having no consistent relationship to the cardia.)

Botha[4] emphasized the anatomic difference between the sliding hiatal hernia of infancy and that of adults. The former is

present at birth as a result of a congenitally short esophagus or a congenitally malformed or underdeveloped diaphragm; the latter is seen in the later decades of life as a result of degenerative changes of normal hiatal structures. The thin, degenerated phrenoesophageal membrane found in adult hiatal hernias does not influence the anatomic appearance seen on roentgenograms or place tension on the lower esophageal sphincter; some investigators consider the membrane in congenital hiatal hernia sufficiently developed to pull on the lower esophageal sphincter in its intrathoracic position[13] and affect the roentgenologic appearance[28] (other authorities[14,23,30] find the membrane at operation to be thin and atrophic).

Manometric studies of esophageal pressures in infants[8,33] and in adults[15] have clearly demonstrated that: (1) a physiologic lower esophageal sphincter exists which is responsible for gastroesophageal competence (with or without a hiatal hernia); and (2) abnormal gastroesophageal reflux is associated with a markedly reduced pressure of the lower esophageal sphincter.

The manometric pressure tracings showed the lower esophageal sphincter to be located at or above the "effective diaphragmatic hiatus" (E.D.H.) in normal infants and at a more cephalic position in infants with a hiatal hernia.[8,33] In addition, it was found that the resting tonus of the L.E.S. of infants with chronic gastroesophageal reflux was uniformly lower (1.9 ± 2.0 mm. Hg) than that of control infants (4.6 ± 2.5 mm. Hg).[34] (Similar studies in normal adults show that the L.E.S. is located from 1.6 cm. below to 2.4 cm. above the E.D.H. and has a resting tone of 5.7 ± 3.0 mm. Hg.)[33]

These anatomic dissections and physiologic measurements indicate that the roentgenologic demonstration of: (1) a segment of stomach above the diaphragm; (2) abnormal gastroesophageal reflux; or (3) a persistently wide esophageal hiatus should always be considered significant when found in an infant.

METHOD

The procedure used in the pediatric patient to demonstrate hiatal hernia and/or gastroesophageal reflux consists of a detailed study of the gastroesophageal region added to the routine upper gastrointestinal series. Indications for this additional study are: (1) appropriate clinical history (vomiting, dysphagia, failure to gain weight, gastrointestinal bleeding, anemia, repeated pulmonary infections); or (2) observation of an abnormality of the cardioesophageal junction during a routine fluoroscopy.

The hiatal hernia-reflux examination immediately follows completion of a routine upper gastrointestinal series fluoroscopy and begins with the patient supine or slightly Trendelenburg in position. (If the gastric fundus is not filled with barium, additional contrast should be given.) A spoonful of barium (Barosperse® Esophageal Cream*) is then given and the movement of contrast through the esophagus is fluoroscopically observed—especially noting the inferior esophageal sphincter and its level relative to the diaphragm.

When satisfactory mucosal coating is seen, multiple spot film roentgenograms of the cardioesophageal region are taken in the anteroposterior and slight right and left anterior oblique projections. A second spoonful of thickened barium is given, the child is immediately turned into the horizontal prone position, and multiple spot film roentgenograms are taken in the posteroanterior and slight right and left oblique position. These supine and prone spot film roentgenograms are mucosal views designed to show (1) the junction between the esophageal and gastric folds and (2) the location of this junction relative to the diaphragm. Allowing the infant to nurse on a sugar nipple or having the older child undergo "dry swallows" often assists in obtaining optimal mucosal detail.

The patient is then turned back into a horizontal supine position and evidence of spontaneous gastroesophageal reflux or re-

* Mallinckrodt Pharmaceuticals, St. Louis, Mo.

flux secondary to increased intra-abdominal pressure (using manual pressure on the stomach) is noted to be present or absent.

After the initial fluoroscopy and standard overtable roentgenograms are taken, the child is held in the erect (preferably), prone or right lateral decubitus (right side down) position for at least 30 minutes. At this time a supine roentgenogram of the abdomen (including the distal thoracic esophagus) is obtained and the patient is placed again into the erect, prone or right lateral position. If contrast material is seen in the esophagus on this roentgenogram in an initially negative study, the child should be held erect until he or she can be refluoroscoped. Often reflux can be seen immediately after the patient is replaced into the supine position for fluoroscopy. It is frequently possible to demonstrate a hiatal hernia at this point (with or without another swallow of thickened barium) even though the initial fluoroscopy was negative.

Patients vary in their roentgenologic manifestations from those with severe gastroesophageal reflux found during a routine study (invariably infants) to those who require an extensive study including several fluoroscopies to document a hernia or reflux (minimal or intermittent). However, the majority of patients are those in whom a gastroesophageal abnormality can be demonstrated by the hiatal hernia-reflux procedure but not by the standard upper gastrointestinal study.

ROENTGENOLOGIC CRITERIA

As the normal infant drinks from a bottle, the esophagus evenly distends with contrast to the level of the inferior esophageal sphincter which produces a variable constriction of the barium column at the diaphragmatic level (Fig. 2*A*). The cardia is located at or just below the diaphragm and there is a well-defined esophageal hiatus. With passage of the bolus of barium and coating of the mucosa, the esophageal folds are seen to be fewer in number and thinner than the mucosal folds of the stomach.

In the patient with a hiatal hernia, the inferior esophageal sphincter is higher in location (Fig. 2*B*); the esophageal hiatus is persistently wide; and gastric folds are seen above the hiatus of the diaphragm. The roentgenologic appearance in the individual patient depends upon the size of the hiatus, the position of the cardia, the competence of the inferior esophageal sphincter, and the presence or absence of an esophageal stricture.

In the review of our patients, it became clear that each roentgenologic sign represented principally an abnormality of anatomy (hiatal hernia) or physiology (incompetence of the lower esophageal sphincter). Those patients with a congenital hiatal hernia demonstrated one or more of the following signs: (1) an abnormally high position of the inferior esophageal sphincter; (2) a beak formation at the gastric cardia; (3) linear orientation of gastric folds toward the esophagus at the cardia (irregularity of the cardia); (4) visualization of gastric folds above the diaphragm; (5) a funnel formation at the cardia; (6) an air-filled hole at the cardia; (7) an epiphrenic loculus; (8) a distal esophageal web; or (9) the presence of delayed gastroesophageal reflux. In contrast, the signs of gastroesophageal incompetence are: (1) free reflux of air or barium from the stomach into the esophagus; and (2) the finding of initial or delayed gastroesophageal reflux.

The position of the inferior esophageal sphincter is determined fluoroscopically as the patient drinks from a nursing bottle or straw. This constriction (pinchcock) is noted at the diaphragm in the normal infant (Fig. 2*A*); it may be demonstrated at a higher position in the patient with a hiatal hernia (Fig. 2*B*).

The "beak" sign (Fig. 3, *A* and *B*) is seen only in the supine position and appears to be due to a minimal widening of the hiatus permitting barium to slightly open the cardia. It was observed in 14 patients and always with one or more additional signs. A variation of the "beak" sign is the "irregular cardia" sign (Fig. 4, *A–C*). This

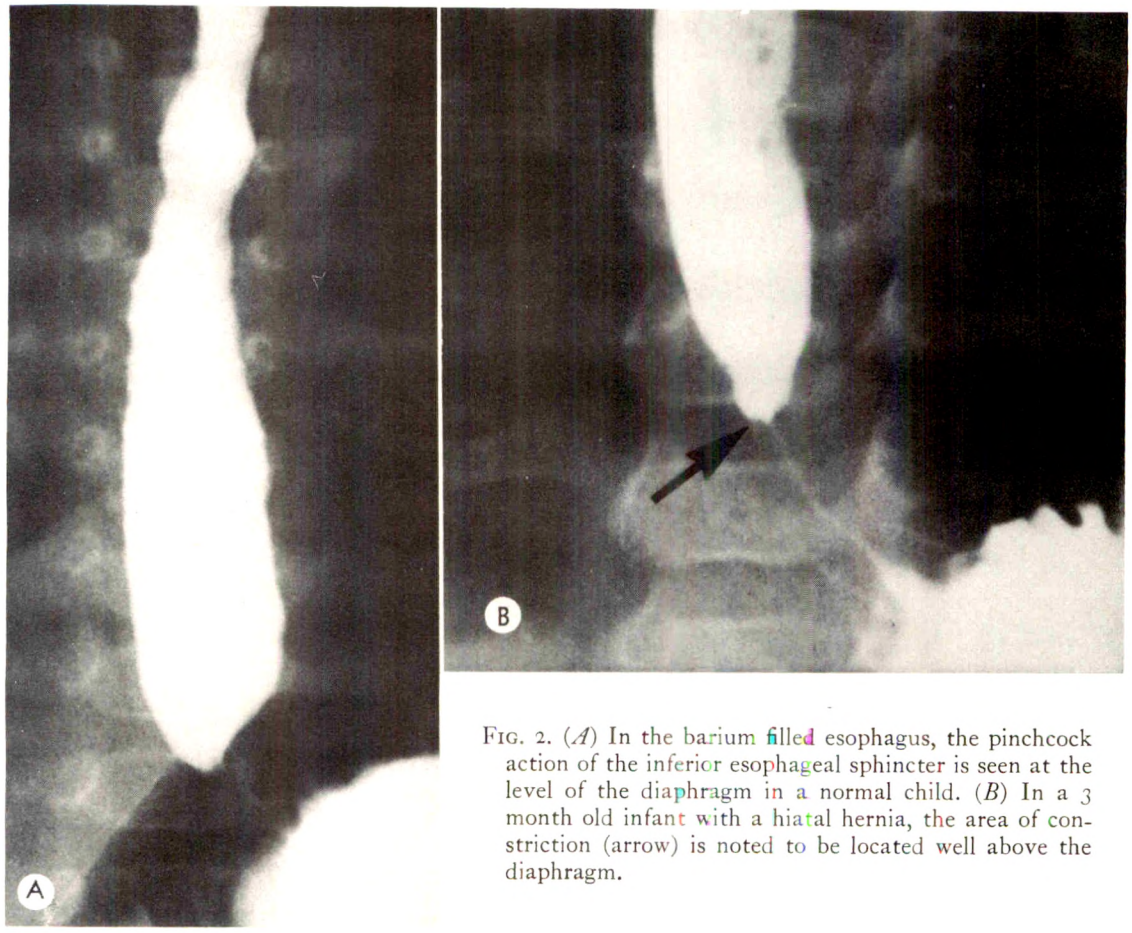

Fig. 2. (*A*) In the barium filled esophagus, the pinchcock action of the inferior esophageal sphincter is seen at the level of the diaphragm in a normal child. (*B*) In a 3 month old infant with a hiatal hernia, the area of constriction (arrow) is noted to be located well above the diaphragm.

also depends on the supine position and is due to an orientation of the gastric folds at the cardia towards the esophagus, thereby interrupting the normally continuous curve of the cephalic end of the stomach. This sign was found in 26 patients, 25 of whom had additional signs.

As the cardia slides to a supradiaphragmatic position, gastric folds can be identified above the diaphragm—the "gastric fold" sign (Fig. 5, *A* and *B*). This was noted in 57 patients. In 56 cases other signs were present; in 1 case it was the only evidence of herniation. With a larger esophageal hiatus, the "funnel" sign (Fig. 6, *A* and *B*) could be identified with the cardia at the apex and hiatus at the base. This sign was noted in 52 patients. It was combined with other signs in 47 cases and was the only sign in 5 instances.

The "hole" sign (Fig. 7) is found in the prone position as a result of air distending the small segment of the stomach herniating through the hiatus. It replaces the mucosal rosette of the normally located cardia and was found in 6 patients—all of whom also had the "funnel" sign.

The "epiphrenic loculus" appears to represent the most advanced degree of herniation (Fig. 8, *A* and *B*). This sign occurred in 40 patients and was associated with other signs in all cases. (Ballooning of the loculus characteristic of the adult form of sliding hiatus hernia was noted in only 1 patient [Fig. 9]. This hernia was not congenital but secondary to repair by primary anastomosis of an esophageal atresia with an extensive defect.)

A distal esophageal web was found in 1 patient (Fig. 10) who also had an epi-

phrenic loculus. (His clinical symptoms responded promptly to medical therapy.)

Free reflux of barium and/or air (Fig. 11, *A* and *B*) occurred in 8 patients. In 5 infants the amount of reflux and cardioesophageal incompetence corresponded to that described in patients with "chalasia." Delayed reflux (Fig. 12, *A* and *B*) was noted in 18 patients and consisted of the demonstration of barium in the esophagus on a supine roentgenogram following a minimum period of 30 minutes in the erect (preferably), prone or right lateral position. It occurred alone in 4 cases and with other signs in 14 cases.

Demonstration of a "beak," irregularity at the gastric cardia or high position of the inferior esophageal sphincter is presumptive or suggestive evidence of a congenital hiatal hernia. (For reasons noted below, we include the finding of delayed reflux as a fourth presumptive sign.) The finding of one or more suggestive signs during fluoroscopy or on follow-up roentgenograms is an indication for further and more detailed examination of the cardioesophageal region in an effort to demonstrate one or more of the definitive signs ("funnel" sign, "hole" sign, supradiaphragmatic gastric folds or epiphrenic loculus) which will establish the presence of a congenital hiatal hernia.

The finding of free reflux and initial or delayed reflux indicates cardioesophageal incompetence which is severe, slight or intermittent, respectively. Free reflux of barium or air without demonstration of a hiatal hernia was considered to be due to a persistent relaxation of the cardia resulting from a temporary neuromuscular aberration by Neuhauser and Berenberg[26] who coined the term "chalasia" for the entity; Astley and Carré[1] felt that chalasia consisted of a partial thoracic stomach in which the roentgenologic localization of the cardia was uncertain. The anatomic abnormality in these patients remains in doubt. However, the clinical findings, evolution, and management of chalasia appears to be identical to that of hiatal hernia and may well be considered one form of the "Hiatal Hernia-Reflux Syndrome."

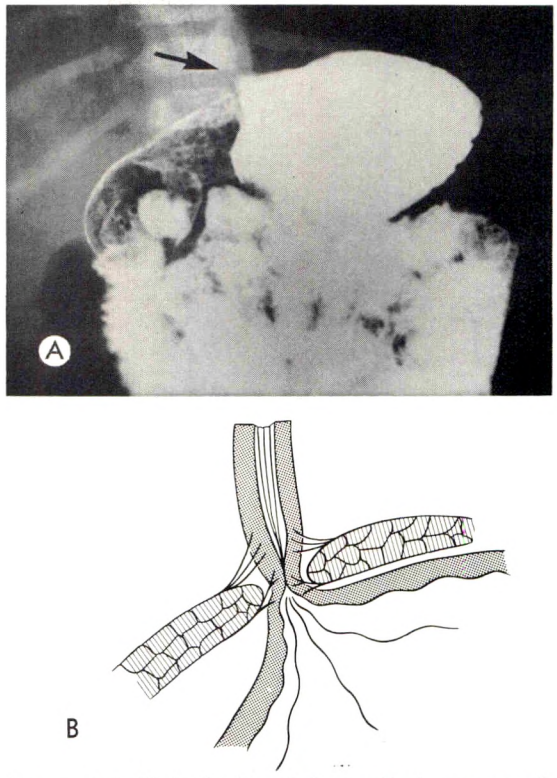

Fig. 3. (*A*) Slight laxity of the cardia in a 2 month old female infant presenting with vomiting allows barium to enter the cardia forming the "beak" sign (arrow) in the roentgenogram. (*B*) The corresponding anatomic changes are diagrammed.

Delayed reflux, when seen in a patient whose initial roentgenograms and fluoroscopy are normal, is an indication for additional fluoroscopic study. Since one or more definitive signs of congenital hiatal hernia have invariably been demonstrated at the repeat fluoroscopy, we consider delayed reflux as a suggestive sign of hiatal hernia. (The 4 patients with delayed reflux alone were identified during our review and were originally reported as normal studies.)

CLINICAL-ROENTGENOLOGIC CORRELATION

Of 83 patients with positive roentgenologic studies, there were 7 who were lost to follow-up and have been excluded from the study. The remaining 76 patients were then grouped by clinical criteria into 44 patients having symptoms from the

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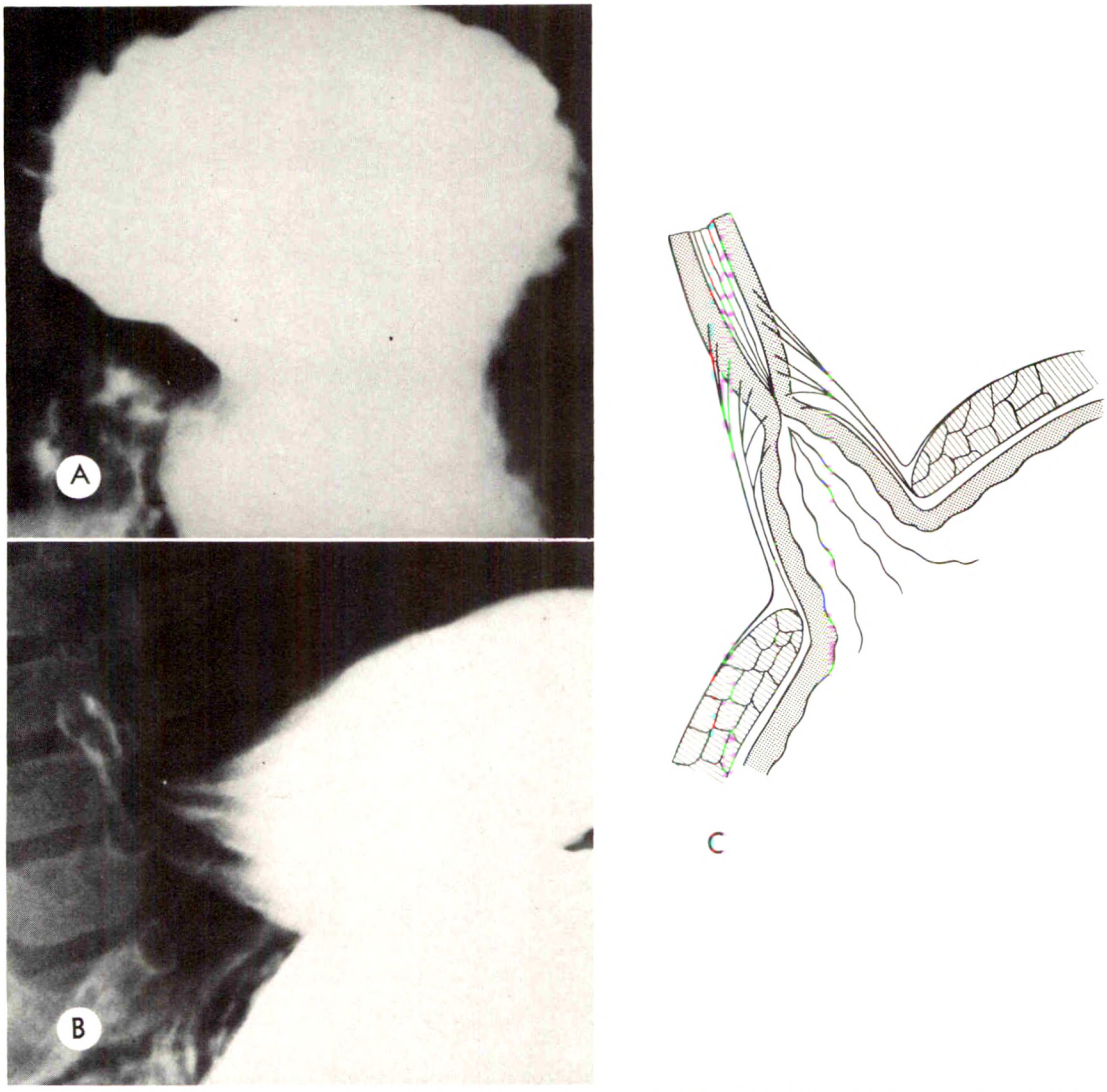


Fig. 4. (*A*) The 30 minute post-fluoroscopic film in a 4 month old male infant with the chief complaint of persistent vomiting shows irregularity of the gastric cardia with linear streaks of barium extending toward the esophagus. (*B*) Re-fluoroscopy with manual compression of the stomach at that point permitted better distention of a small hiatal hernia with minimal reflux into the esophagus. (*C*) Diagram depicts the anatomic changes in *B*.

hiatal hernia and/or reflux and 32 patients in which the roentgenologic abnormality was an incidental finding.

The roentgenologic criteria described previously were listed for each patient and the resulting frequency of occurrence for each sign was determined for both clinical groups (Table II). This demonstrated that roentgenologic findings alone cannot be used as a basis of patient evaluation but must be fully correlated with the clinical status to be meaningful.

In our own group of patients, this correlation was found to be of extreme importance and clearly indicated the significance of the roentgenographic demonstration of a hiatal hernia and/or reflux in each patient. It was found that the presenting symptom of vomiting—especially during the first year of life—with no other demonstrable cause (*e.g.*, pyloric stenosis, Hirschsprung's disease, gastroenteritis) was invariably re-

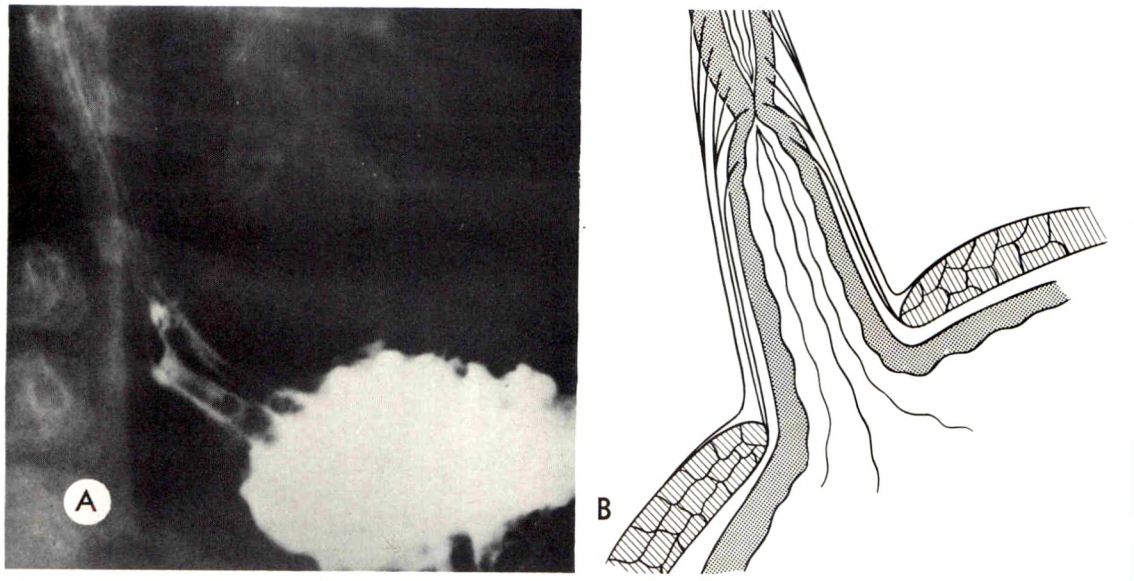


Fig. 5. (*A*) Gastric folds above the diaphragm can be identified in the roentgenogram of a 10 month old male infant with vomiting. (*B*) The influence a phrenoesophageal membrane may have on the roentgenographic appearance of a hernia is demonstrated.

lated to the hernia and responded well to medical therapy. The clinical presentation of dysphagia, upper gastrointestinal bleeding, and/or anemia or Sandifers' syndrome also appeared to be related to the hernia in the initial and follow-up evaluation of our patients.

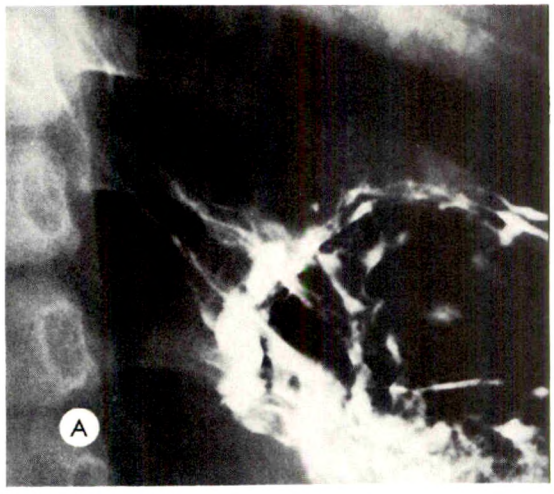
The symptoms of pain or burning in the epigastric or substernal area typical of the adult with a hiatal hernia was the chief complaint of almost all of the older children. This has raised the possibility that some congenital hiatal hernias persisting on roentgenologic examination (*c.f.* below) cause symptoms in late childhood or adult life. Another important manifestation recognized with increasing frequency is the pulmonary complication of reflux with aspiration. This is of major significance in small infants and may be one possible cause of "crib deaths" in apparently healthy infants.

DISCUSSION

A knowledge of the natural history of congenital hiatal hernia in the untreated patient is essential to understanding the normal evolution of the disease and to alterations of this pattern resulting from medical and/or surgical therapy.

In his classic study of untreated patients, Carré[9] found that symptoms invariably began early in infancy. Vomiting with the onset occurring in the first 4 weeks was the most common historical finding. At the time of weaning, 60–65 per cent of the patients improved or became completely asymptomatic. Of those who had no improvement or whose symptoms became worse with weaning, 5 per cent developed esophagel strictures and the remaining 30–35 per cent developed no stricture but continued to have moderate or frequent vomiting and/or dysphagia which persisted to at least 4 years of age. In this study a very small group of infants died as a result of infection, severe malnutrition, and electrolyte disturbance.

Postural therapy in the treatment of these patients was introduced in the early 1950s with a striking result. (This treatment consists of placing the infant into a sitting position with the trunk forming an angle of 60 degrees or more from the horizontal. This position is continued on a 24 hour basis to the age of 1 year or until the



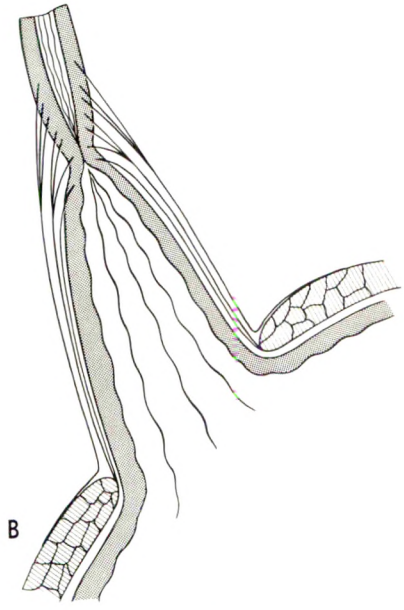


Fig. 6. (*A*) Roentgenographic appearance of the "funnel" sign in a 4 year old boy with Sandifers' syndrome. (*B*) The anatomic changes which may be responsible for this appearance are shown.

patient is free of symptoms at least 6 weeks.) With this positional therapy, 2 clinical groups of patients were noted (excluding cases of esophageal stricture).[10] The major group (about two-thirds of the patients) became free of symptoms within 3 months of the start of therapy in contrast to an average age of 2 years in the untreated group;[9] the smaller group (about one-third of the total) responded much more slowly.[10] When compared to the natural history of the untreated patient,[9] adequate postural therapy appeared to accelerate the natural evolution of the disease. No change in the incidence of esophageal stricture was noted with positional therapy. This may be due to the rapidity with which stricture may form in the susceptible patient.

As patients were followed to complete disappearance of all clinical symptoms, Carré and Astley[11] and other authors[5,7,35] found that a hiatal hernia could still be demonstrated roentgenographically. It was found (excluding patients with esophageal strictures) that only 1 out of 3 patients had a roentgenologic "cure"[11] despite disappearance of clinical symptoms.

The evaluation of hiatal hernia and/or gastroesophageal reflux in the pediatric age group must consider the following factors: (1) a hiatal hernia at this age is present at birth due to abnormal development of the esophageal hiatus.[4] In those patients with formation of an adequate phrenoesophageal membrane, it (a) acts to prevent lateral expansion of the herniated portion of the stomach and (b) places tension on the lower esophageal sphincter which may cause re-

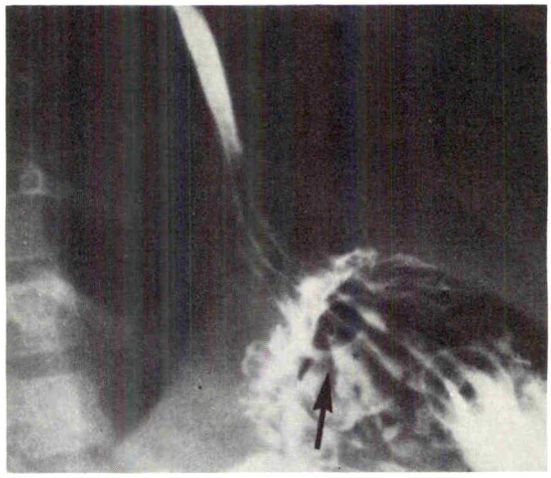


Fig. 7. Demonstration of the "hole" sign (arrow) produced by air filling the hiatal hernia and barium coating the stomach wall at the level of the esophageal hiatus. The patient is a 7 month old male infant admitted for vomiting.

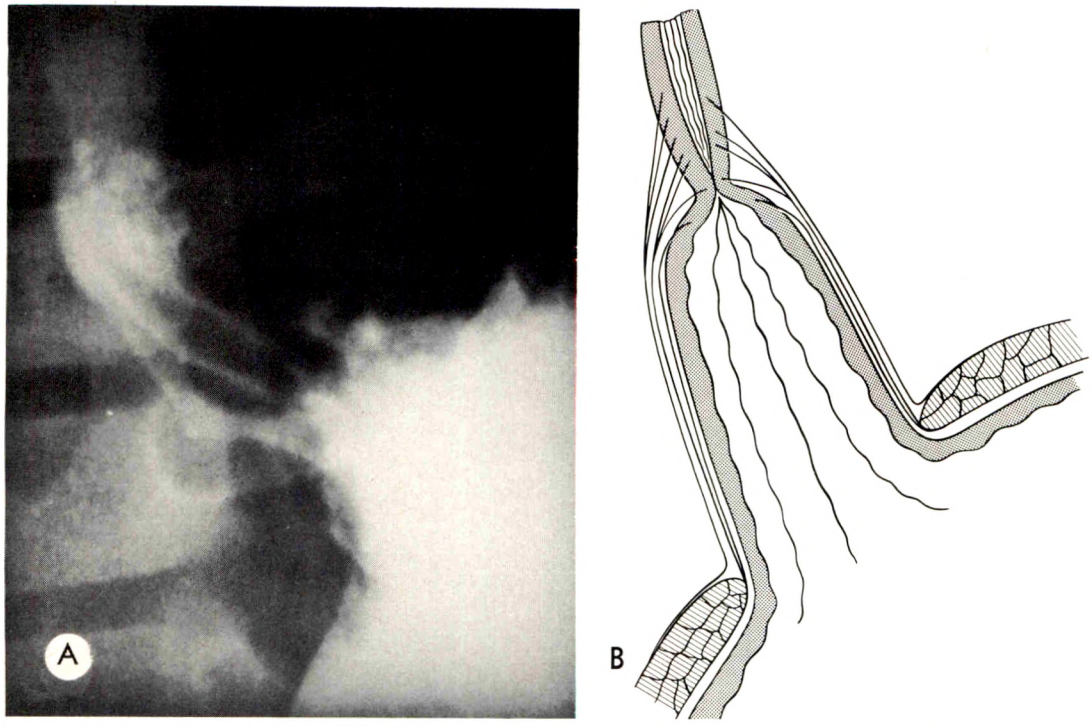


Fig. 8. (*A*) The "epiphrenic loculus" as seen on a roentgenogram, and (*B*) an anatomic drawing. This is similar to the appearance of a small sliding hiatal hernia in an adult.

flux;[13] (2) the lower esophageal sphincter usually prevents reflux despite an intrathoracic location, increased tension of the phrenoesophageal membrane on the sphincter,[13] and loss of normal crural support of the diaphragm; (3) the traditional prone position (a form of positional therapy) of the American infant may prevent clinical symptoms in many infants who have the anatomic abnormality; (4) the natural history of the disease is that of complete disappearance of symptoms in 90–95 per cent of the patients with or without treatment; (5) the roentgenographic diagnosis is much more difficult in the pediatric patient than in the adult and requires (a) an understanding of the anatomic differences between the congenital hernia of a child and the acquired hernia of the older adult and (b) special techniques utilizing multiple spot film roentgenograms (*c.f.* above) or cinefluorography;[19] (6) it is of little importance whether a patient has a congenital hernia with reflux or reflux without herni-

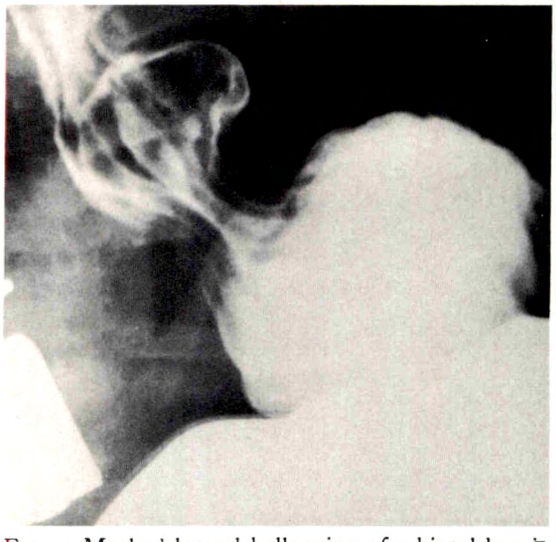


Fig. 9. Marked lateral ballooning of a hiatal hernia found while examining an 8 month old female infant for the status of her anastomosis following repair of a congenital esophageal atresia of considerable length with surgical division of the phrenoesophageal membrane. Note marked cardioesophageal incompetence with reflux of barium and air into the esophagus. Subsequently the patient developed symptoms of esophagitis and is being considered for surgical repair of the hernia.

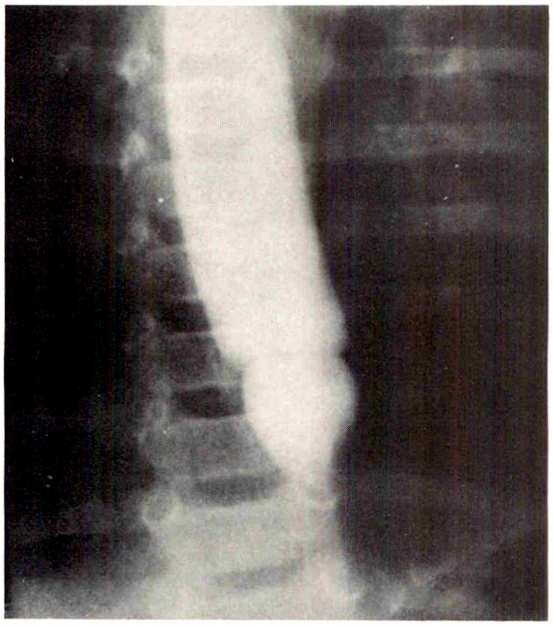


Fig. 10. With distention of the esophagus, a sharply defined concentric narrowing of the barium column is found in a 3 month old male infant examined because of vomiting. This may represent an example of Schatzki's ring.

ation as the clinical symptoms depend upon abnormal gastroesophageal reflux in both cases and the treatment, complications, and indications for surgery are identical; (7) roentgenographic findings of a hiatal hernia persist in the majority of children even after symptoms due to the hernia have entirely resolved.

SUMMARY

During a study period from July, 1971 through March 1973, a review of 285 roentgenologic examinations of the esophagus and upper gastrointestinal tract showed a hiatal hernia and/or abnormal gastroesophageal reflux in 83 infants and children.

The technique of demonstrating hiatal hernia and/or abnormal reflux in the pediatric patient is described and the criteria used in diagnosis are illustrated, analyzed, and correlated with the clinical symptomatology.

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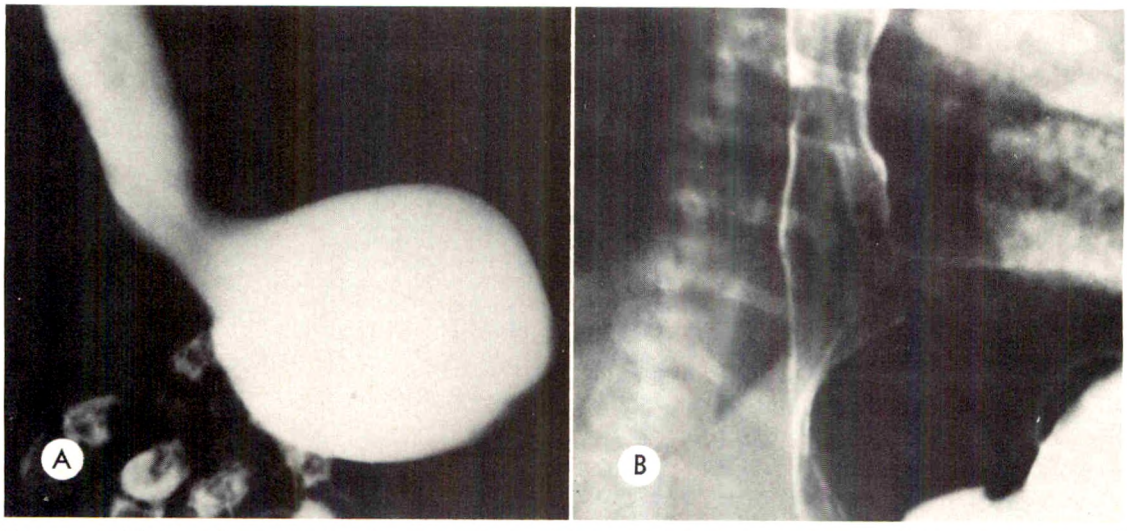

Fig. 11. (*A*) Free reflux of barium in the supine position, and (*B*) air in the prone position are evidence of severe cardioesophageal incompetence. A slight limitation of esophageal dilatation can be seen and appears to represent the lower esophageal sphincter.

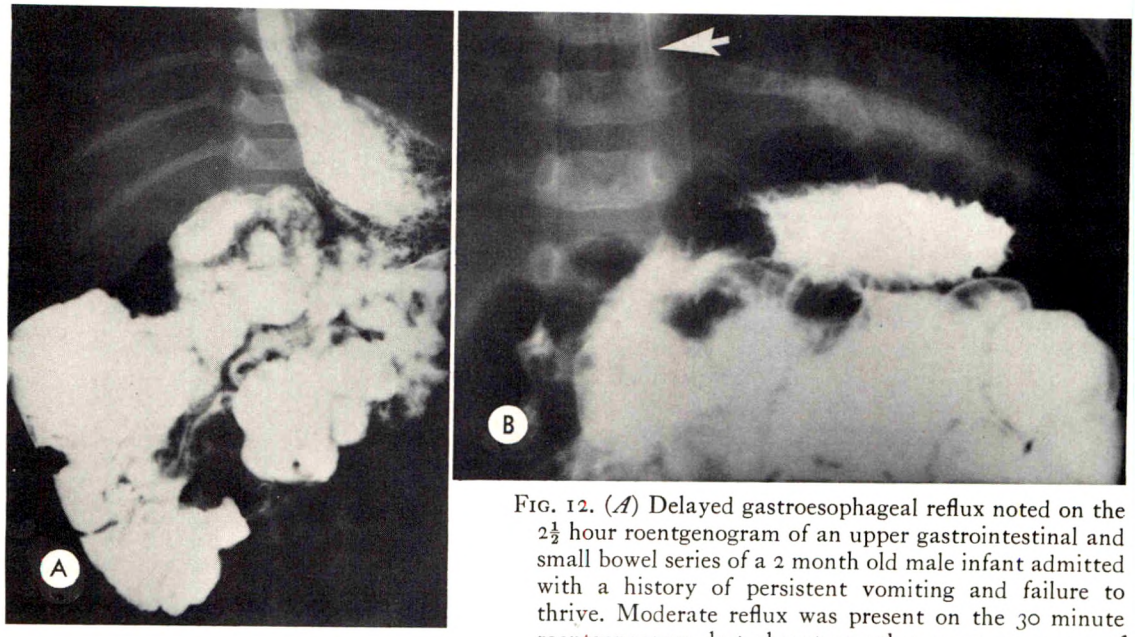

Fig. 12. (*A*) Delayed gastroesophageal reflux noted on the 2½ hour roentgenogram of an upper gastrointestinal and small bowel series of a 2 month old male infant admitted with a history of persistent vomiting and failure to thrive. Moderate reflux was present on the 30 minute roentgenogram, but absent on other roentgenograms of the small bowel follow-through, indicating the intermittent character often found in reflux. (*B*) Minimal delayed reflux is demonstrated on the 30 minute roentgenogram of a 2 month old female infant presenting with vomiting. Delayed reflux is typically minimal in degree and, therefore, easily overlooked.

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Table II

Correlation of Clinical and Roentgenologic Signs

Sign	Symptoms Unrelated (32 Patients)		Symptoms Related (44 Patients)	
	No. of Patients	Per Cent	No. of Patients	Per Cent
Beak	5	16	9	20
Irregularity of Cardia	11	38	11	25
Supradiaphragmatic Gastric Folds	22	69	30	68
Funnel	15	47	31	70
Hole	1	3	3	7
Epiphrenic Loculus	17	53	19	43
Free Reflux of Barium and/or Air	2	6	6	14
Web	0	0	1	2
Delayed Reflux	9	28	9	20

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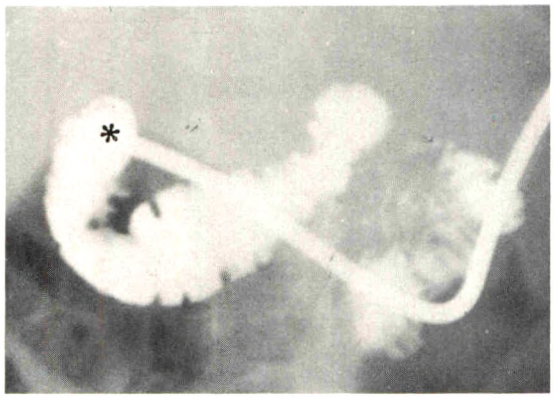

Fig. 1. Case 1. An injection of barium through the gastrostomy showed that the tip of the catheter was in the duodenal cap. Identical findings were encountered in Patients 2–5.

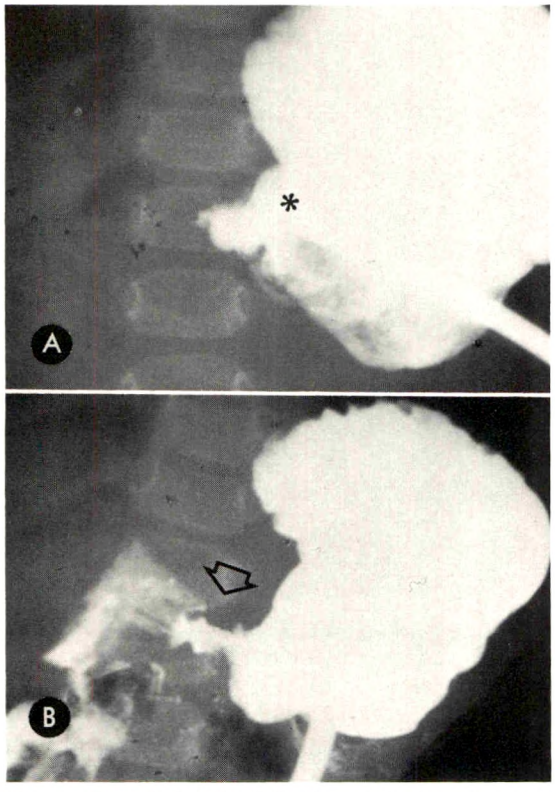

Fig. 2. Case 6. (*A*) An injection of barium through the gastrostomy showed that the tip of the catheter was wedged in the antrum causing a high degree of obstruction. (*B*) A similar injection immediately following reposition of the catheter showed an edematous antrum with continuing partial obstruction (arrow). These changes were still present 10 days later, but no longer visible 3 weeks later.

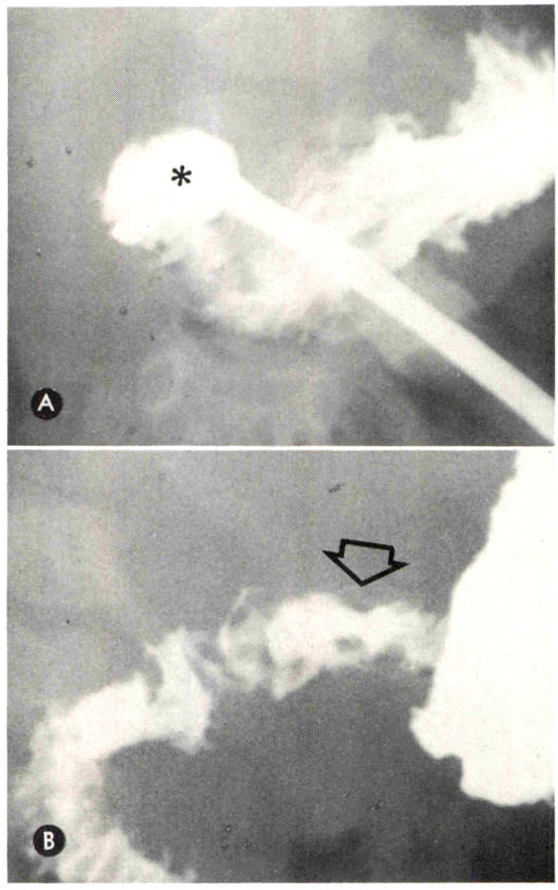

Fig. 3. Case 7. (*A*) An injection of barium through the gastrostomy showed that the tip of the catheter was wedged in the antrum causing a high degree of obstruction. (*B*) A similar injection following reposition of the catheter showed an edematous, partially obstructed antrum (arrow).

usually without difficulty. In the case of a Foley catheter, the balloon should be deflated before manipulation. A second injection of contrast material is indicated to check the new position of the tube and to evaluate the status of the stomach and duodenum.

A finding apparently not previously reported was encountered in 4 of our patients (Cases 6, 7, 8, and 9). It consisted of marked edema of the antrum caused by prolapse of the catheter, producing an additional obstruction.

One of the patients (Case 8) developed hypertrophic pyloric stenosis. Similar observations have been reported by Bigger[1] and Leven *et al.*[8] In the 3 infants reported

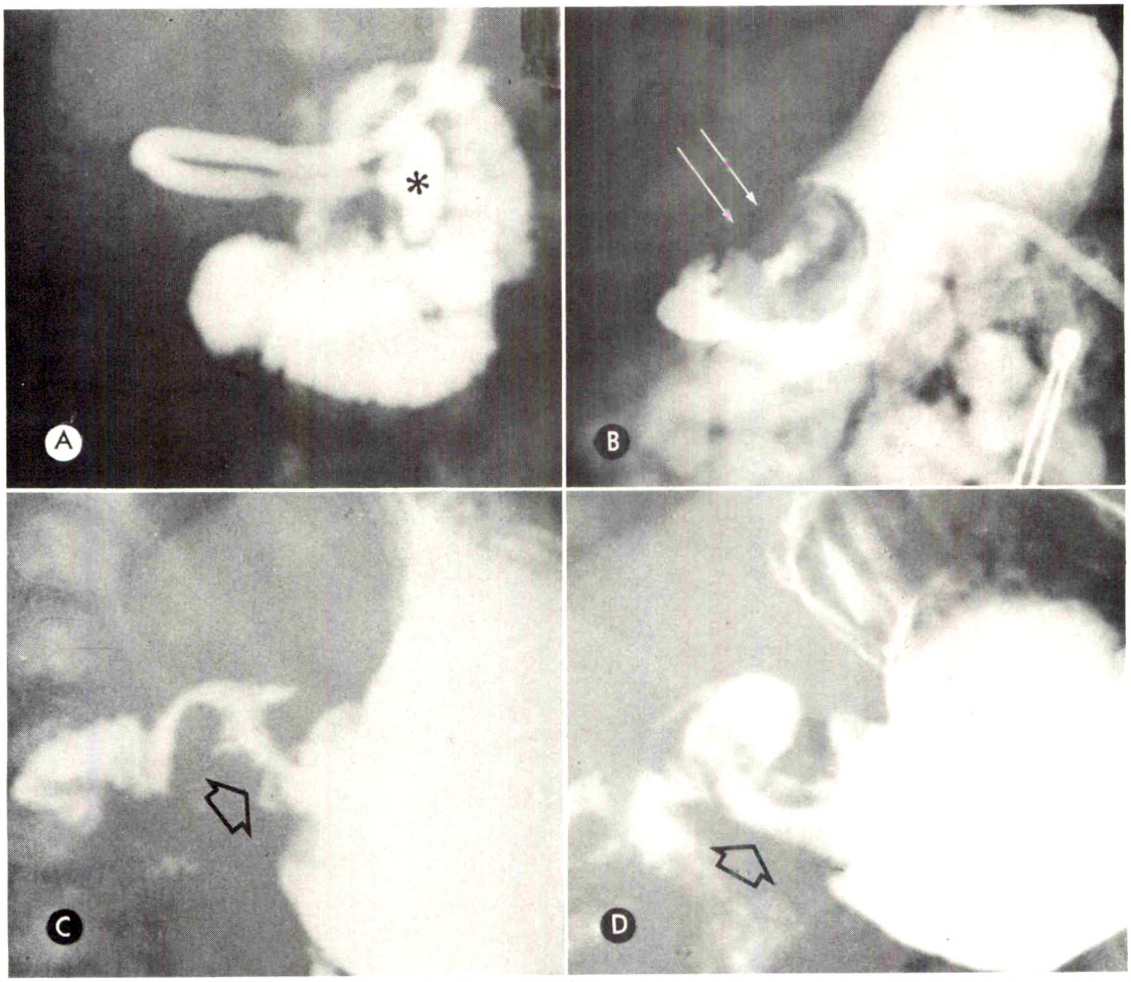

Fig. 4. Case 8. (*A*) An injection of barium through the gastrostomy showed that the tip of the catheter was in the distal transverse duodenum. (*B*) A similar injection immediately following reposition of the catheter showed an extreme degree of edema at the gastric outlet with complete obstruction (arrows). (*C*) A re-examination 2 days later continued to show antral edema (arrow). (*D*) Another barium study 7 days later suggested the presence of hypertrophic pyloric stenosis confirmed at laparotomy (arrow).

by Bigger,[1] the gastrostomy tube—apparently a straight catheter—had been placed intentionally through the pylorus and around into the jejunum in an attempt to prevent regurgitation of the formula; it is of interest that all 3 of these infants were female and were in the hospital at the same time. The position of the catheter in the 2 infants mentioned by Leven *et al.*[8] is not known. Although the cause for this complication is unknown, it is tempting to postulate that it might have been the irritation caused by the tube that led to the local muscular hypertrophy.

The symptoms usually subside promptly following reposition of the catheter except in the case of marked antral swelling, when they improve more slowly, or when hypertrophic pyloric stenosis develops.

Probably, the most important cause of the prolapse is an inadequate anchorage of the tube to the abdominal wall. Special devices and techniques have been recommended for the purpose of maintaining the stomach against the anterior abdominal wall and of preventing prolapse of the tube.[9–11]

The parents should be advised of the possibility of this complication and of its symptoms. Marking the tape at a given

distance from the skin or providing the parents with tubing of similar length for measurements of extra-*versus* intra-abdominal segments may also be helpful for an early diagnosis of the complication.

SUMMARY

An important complication of gastrostomy is prolapse of the catheter in the antrum of the stomach, or in the duodenum.

The prolapse usually causes gastric obstruction or bleeding, diarrhea after tube feeding, and other symptoms. The symptoms subside promptly in most cases following repositioning of the catheter.

Nine new instances in children are reported.

A complication of the prolapse not previously emphasized is marked swelling of the antrum which improves slowly following repositioning of the catheter.

One of the infants developed hypertrophic pyloric stenosis.

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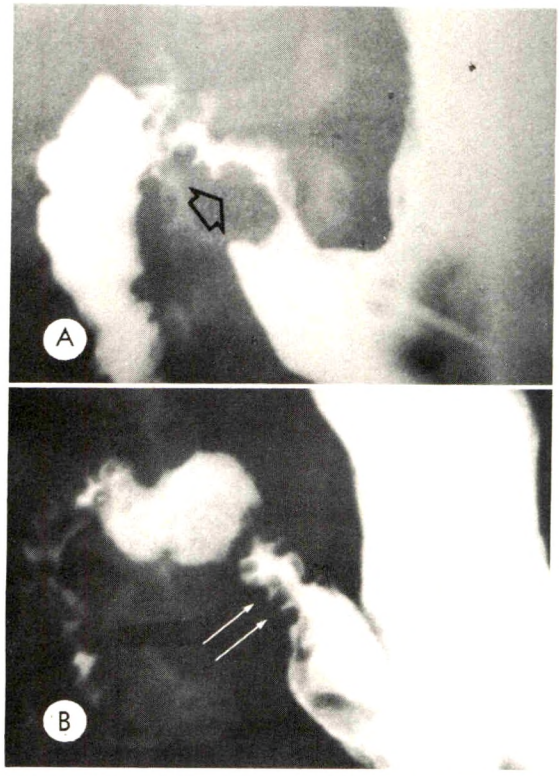

Fig. 5. Case 9. On admission the gastrostomy tube could not be mobilized and when irrigated only clear fluid return was obtained. When the tube was finally taken out, a gush of blood was observed. Another Foley catheter was introduced and an injection of barium through the new tube showed considerable edema of the antrum (*A*, arrow). A re-examination 6 weeks later continued to show some antral edema (*B*, arrows).

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UNUSUAL FEATURES AND COMPLICATIONS OF BEZOARS IN CHILDREN*

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BEZOARS are uncommon foreign bodies usually composed mainly of hair (trichobezoar) and food particles found impacted and forming a cast in the stomach or small intestine. Bezoar derives from the Persian word Padzahr meaning protection against poisons. Other less common forms of gastric bezoars that have been reported include those composed of vegetable fibers (phytobezoar), antacids, pitch, animal fats, shellac and latex.[2] Historically the use of animal bezoars to ward or cure ailments dates back to the 12th century B.C., when it had variously been advocated as an antidote for poisons, to prevent dysentery, plague, leprosy and cure gallbladder pain. The bezoar was so popular a remedy that those who could not afford to buy one could rent them by the day.[5]

We present 7 patients with bezoars (Table 1) with detailed case histories in 3. Of the 6 who had trichobezoars, 5 developed complications, which included extension to the jejunum, intussusception, hypoproteinemia secondary to malnutrition because of a large bezoar, bowel obstruction, and fatal perforation of the stomach. The sixth patient had a trichobezoar which passed per rectum. The seventh patient had a phytobezoar treated conservatively for 2 years. The 7 patients ranged in age from 15 months to 9 years.

Three patients with complications will be described in detail.

REPORT OF CASES

Case 1. E.W. A 4 year old Black girl was admitted for abdominal pain and vomiting of 1 day's duration. There was a preceding history of anorexia and constipation of 1 week. Since 2 years of age the mother had observed the child habitually pulling her hair. On examination the child appeared well developed and nourished. The hair over the frontal area of the scalp was sparse. In the abdomen, a 3×3 cm. mass was palpable in the left hypochondrium. Another small mass 1.5×2 cm. in size was palpated in the left umbilical area. Both were smooth, non-tender superficial and mobile.

Table I

DATA FROM 7 CHILDREN WITH BEZOARS

Patient	Age	Sex	Clinical Presentation	Unusual Features and Complications
1. E.W.	4 yr.	F	Abdominal pain, vomiting, constipation, palpable abdominal mass	Extension into jejunum
2. S.R.	15 mo.	F	Abdominal pain, vomiting, diarrhea, palpable abdominal mass	Multiple intussusceptions
3. B.W.	6 yr.	F	Fever, vomiting, abdominal distention	Gastric perforation, pelvic abscess; rickets
4. M.R.	5 yr.	M	Edema, hypoproteinemia, microcephalic	Small bowel obstruction; protein losing enteropathy
5. K.B.	9 yr.	F	Abdominal pain, vomiting, abdominal mass	Phytobezoar; patient followed 20 months preoperatively
6. S.W.	4 yr.	F	Vomiting, pain, constipation, palpable mass	Bowel obstruction
7. L.L.	2 yr.	F	Vomiting, anorexia, palpable mass	Bezoar passed per rectum

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Bowel sounds were normal. A plain film of the abdomen demonstrated a radiopaque mass within the stomach. Not only was this confirmed on a gastrointestinal study, but segments of the trichobezoar were also seen in the jejunum suggesting intussusception (Fig. 1). At surgery a large trichobezoar was found in the stomach and extending through the duodenum into the jejunum. The specimen measured 22 cm. in length and 5 cm. in width. She had an uncomplicated postoperative course and was referred for psychiatric evaluation.

Case II. S.R. A 15 month old Black female was hospitalized because of 3 days' history of abdominal pain, vomiting and diarrhea. There was a history of eating hair. The patient was a pale malnourished child with a hard mass the size of an orange in the epigastrium. Hyperactive and some high pitched bowel sounds were heard. Her hemoglobin was 8.2 gm. per cent, hematocrit 34 per cent. Plain roentgenograms of the abdomen demonstrated the mass in the stomach as well as multiple small bowel air fluid levels with an over-all appearance suggesting small bowel obstruction. An upper gastrointestinal series confirmed the presence of the bezoar. At surgery a large comma shaped trichobezoar weighing 80 grams was removed from the stomach; multiple intussusceptions were reduced.

Case III. B.W. A 6 year old Black female was hospitalized for fever, vomiting, abdominal distention, anorexia and constipation of 2 days' duration. Her growth and development had been normal until the age of 10 months when she had her first convulsive seizure. This was followed by frequent seizures and both physical and mental regression. She was unable to walk and was not toilet trained. She had been observed eating anything available. On physical examination she was a toxic appearing, emaciated, mentally retarded child. Her extremities were hypotonic and contractures were present. There were numerous decubiti around the buttocks. She ground her teeth and her tongue protruded. Heart rate was 132, respiratory rate 35, weight 25 pounds, height 100 cm. Head circumference was 52 cm., and abdomen also 52 cm. The abdomen was tense and tympanitic but bowel sounds were present. Supine and upright views of the abdomen disclosed both massive free air and a soft tissue mass visible within the lumen of the

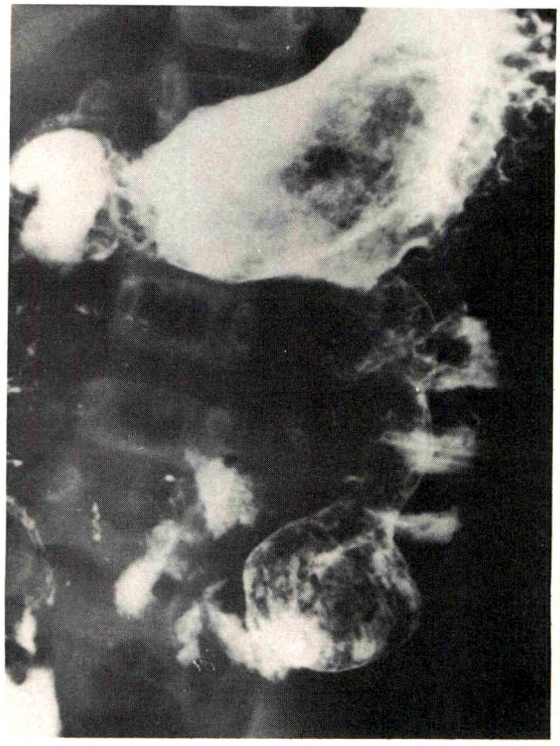

Fig. 1. Case 1. Bezoar is an amorphous radiolucency in the barium-filled stomach and extends to the left into the jejunum as a dumbbell-shaped radiolucent mass.

stomach (Fig. 2). Upper gastrointestinal series demonstrated a large gastric bezoar, and perforations in the posterolateral and superomedial portion of the fundus of the stomach (Fig. 3). Appearance of the second and fourth portion of the duodenum suggested displacement of broken parts of the bezoar. At surgery a 300 gram foul smelling trichobezoar was removed from the stomach. In addition 2 perforations of the anterior wall of the stomach were found (Fig. 4) and a large pelvic abscess was drained. The postoperative course was complicated by pneumonia; *Pseudomonas aeruginosa* was cultured from the sputum and blood. She became increasingly lethargic and was placed on a respirator. Despite this she expired 7 days postoperatively. An autopsy revealed abscesses of both lungs, acute generalized peritonitis, ulcers in the jejunum and rectum, bilateral subdiaphragmatic abscesses and rickets.

DISCUSSION

Complications associated with trichobezoars are frequent. Those that have been

Fig. 2. Case III. Upright roentgenogram of the abdomen shows a bezoar containing calcified debris in the stomach. Free air is seen under the left hemidiaphragm.

reported include extension into the small intestine with obstruction and compression, breaking off of segments with intussusception, necrotic perforations of stomach or small bowel, giant bezoars, gastrointestinal bleeding, nutritional edema, and fistulas.[1–6,8–14]

These complications are related to the impaction of hair and other matter in the stomach. Experimental studies in rabbits done in 1912 have shown that single pieces of hair cannot be moved distally by peristaltic activity.[5] Also, diet has been demonstrated to be a factor with pasty foods, in particular, favoring the formation of hairballs.[7] Once the mass is of sufficient size to prevent passage through the pylorus it grows by accretion. When fragments of a trichobezoar break off and pass the pylorus into the small bowel they may cause obstruction or ulceration. About 10 per cent of patients with trichobezoars have a gastric ulcer. Those associated with perforations carry a risk of very high mortality rate probably due to severe peritonitis.[9,10] DeBakey and Ochsner[5] explained these ulcers on the basis of increased acid secretion. Most ulcers have been described on the lesser curvature.

Five of the 7 children reported, 6 female, 1 male, presented with complications secondary to bezoars varying from extension to the jejunum with intussusception, to perforation of the stomach. This last patient also developed an abscess and peritonitis and subsequently died. One patient had edema and a total serum protein of 4.5 mg. per cent, but no protein in the urine. Work-up for protein losing enteropathy was interrupted when he developed a small bowel obstruction which required removal of his trichobezoar. One week postoperatively the total protein rose to 6.2 mg. per cent. He had been unable to eat for 2 weeks prior to admission because of a large bezoar, and the hypoproteinemia may have resulted from a combination of malnutrition and hypertrophic gastritis with altered absorption from gastric mucosa. Leg edema and hypertrophic gastritis in a patient

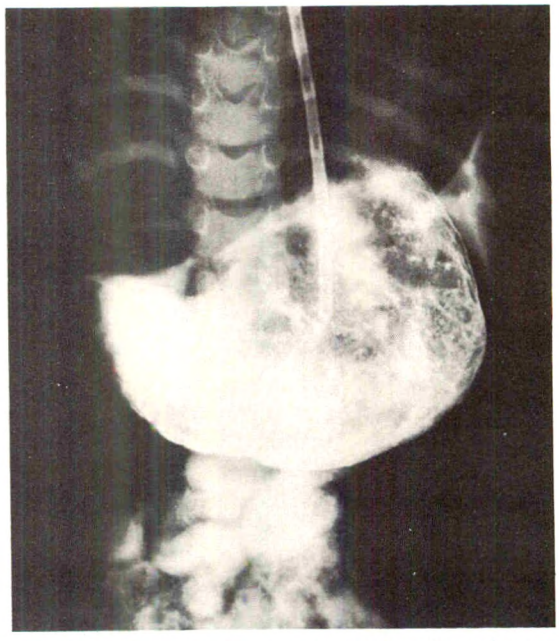

Fig. 3. Case III. Barium study outlines large bezoar in stomach with lateral perforation.

with a gastric bezoar was described in 1921 by Davies.[4] In 1957 Wine[14] reported malnutrition in a young girl with a trichobezoar and in 1966 Valberg *et al.*[12] demonstrated protein losing enteropathy using I^{131} labelled human albumin and polyvinylpyrrolidone in 2 patients. Hypoproteinemia, whatever the cause, disappeared after surgical removal of the bezoar in all cases reported, as was also true in our patient (M.R.).

Hypochromic microcytic anemia was present in all patients. Bacterial overgrowth as a cause of megaloblastic anemia has been reported in combination with trichobezoars,[3,6] but was not seen in any of our children; B_{12} and folic acid determinations when performed were normal.

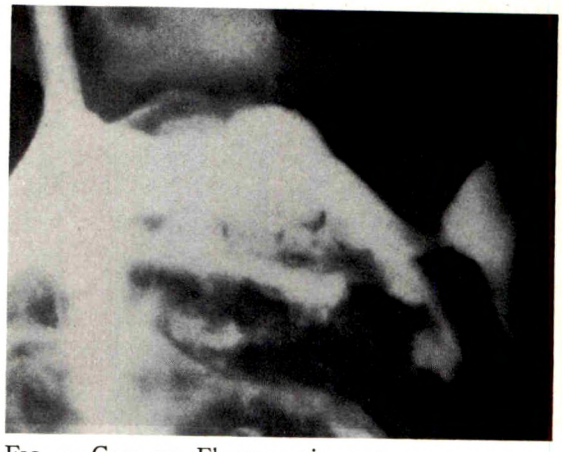

Fig. 4. Case III. Fluoroscopic spot roentgenogram demonstrates 2 localized perforations arising from the fundus of the stomach.

CONCLUSION

All patients had vomiting and abdominal pain as the most common presenting features, although anorexia, nausea, weakness, weight loss and constipation were also commonly seen. One patient unexpectedly passed a bezoar per rectum after a history of vomiting for 1 year. As with many youngsters who have this condition, 2 of ours were mentally retarded, the others in need of psychiatric help. One patient, however, was highly intelligent, receiving A's in all school subjects.

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CASCADE STOMACH*

ROENTGEN APPEARANCE AND SIGNIFICANCE

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ANATOMICALLY, the fundus of the stomach is that portion of the vertical part of the stomach above the level of the cardiac orifice.[6] It has, however, been pointed out that this anatomic usage[3] is not generally adopted by radiologists, who ordinarily speak of the fundus as the expanded upper portion of the stomach without precise definition. Radiologic usage is somewhat clearer in the recumbent position either supine or prone, when the more horizontal expanded uppermost portion of the stomach is angulated on the "vertically" oriented body of the stomach.

In the usual J-shaped stomach, the fundus lies in the same longitudinal axis as the

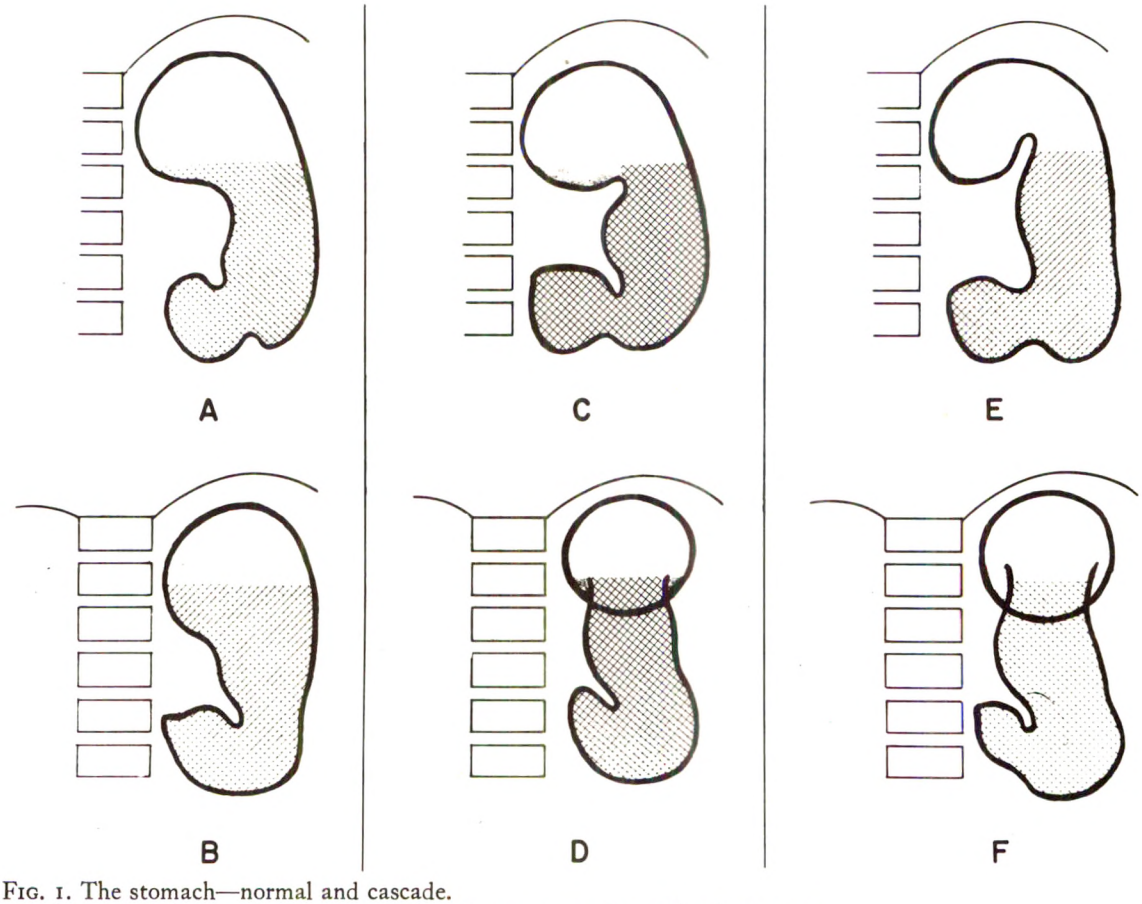

FIG. 1. The stomach—normal and cascade.
(*A* and *B*) Normal stomach, lateral and anteroposterior projections, erect.
(*C* and *D*) Borderline, lateral and anteroposterior projections, erect. Despite the presence of a ridge, there is a single fluid level.
(*E* and *F*) Cascade stomach, lateral and anteroposterior projections, erect. There is a well defined ridge and 2 separate fluid levels.

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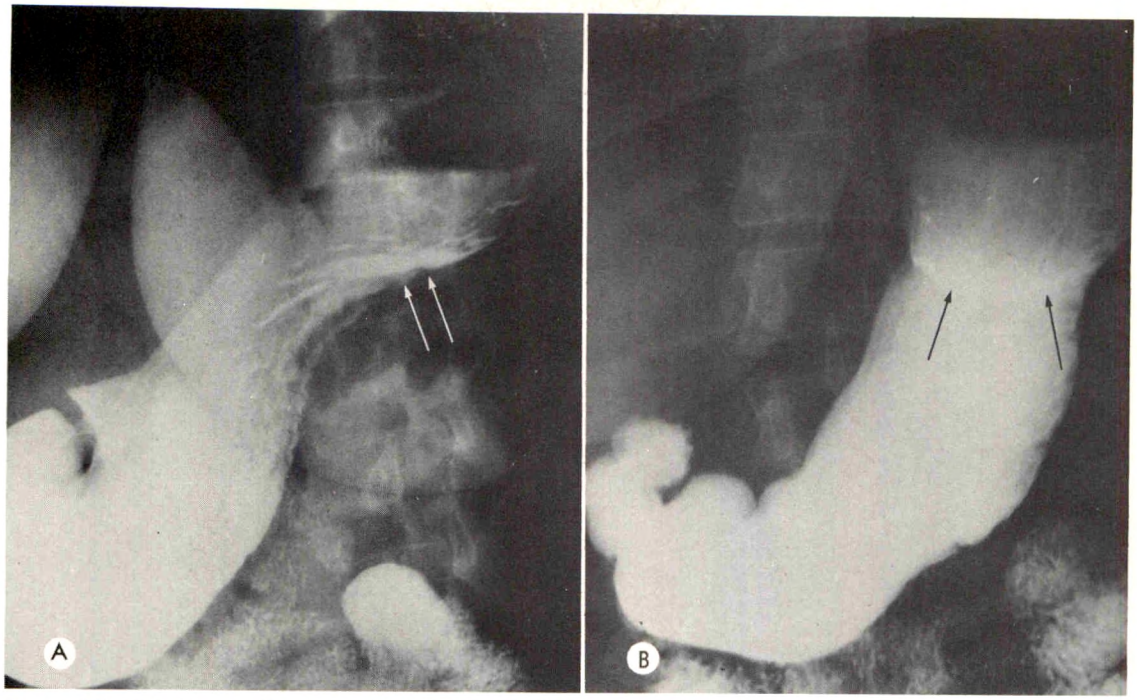


FIG. 2. The filled stomach—erect: borderline cascade.

(*A*) In the left anterior oblique projection, the inferior wall of the fundus is defined by a horizontal "ridge" (arrows) created by the gas distended splenic flexure. (*B*) In the posteroanterior projection, the displacement of the posterior wall by the splenic flexure creates a "pseudoloculus."

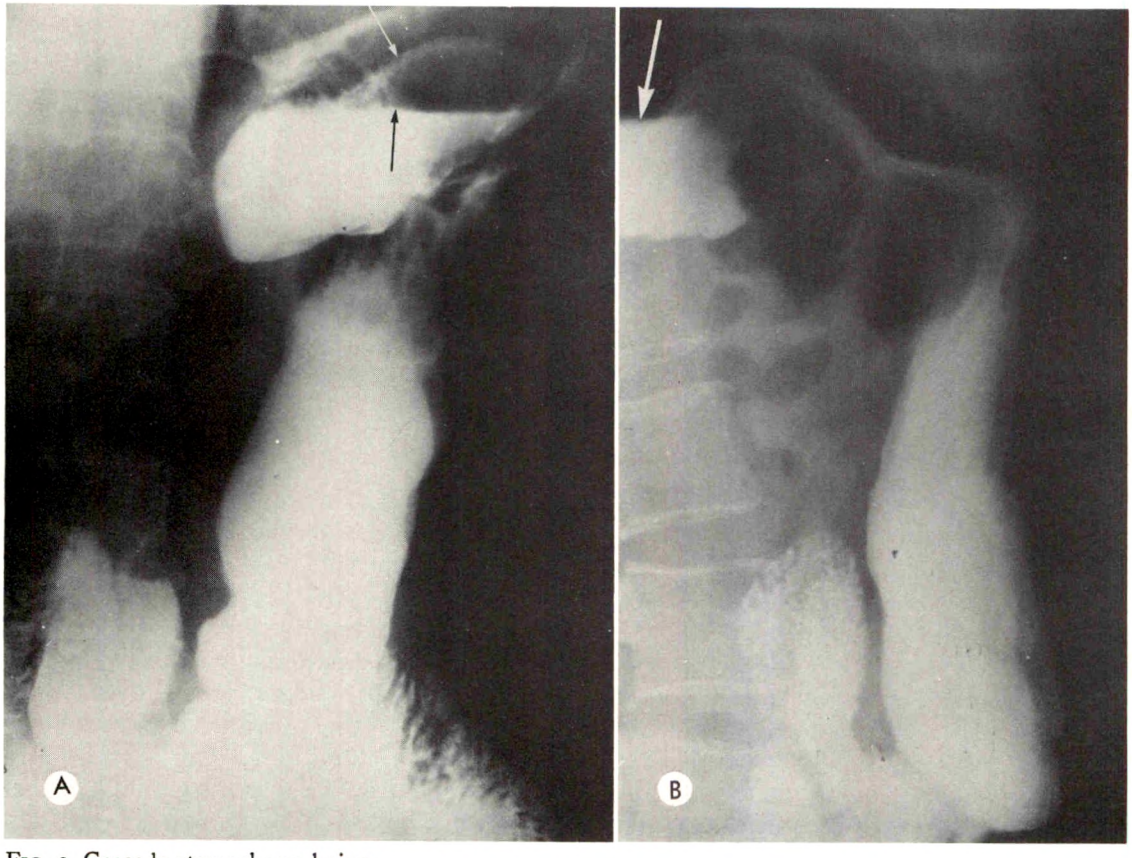


FIG. 3. Cascade stomach: no lesion.

(*A*) The erect posteroanterior projection shows an independent fluid level in the fundus (lower arrow) with overlapping of the fundus and upper part of the body of the stomach. The upper margin of the gas filled splenic flexure (upper arrow) is seen through the fundus. (*B*) The erect lateral view demonstrates posterior loculation of the fundus with an air-barium level (arrow). The gas filled splenic flexure indents the stomach in the region of the "ridge." The body of the stomach is pushed forward and upward. The

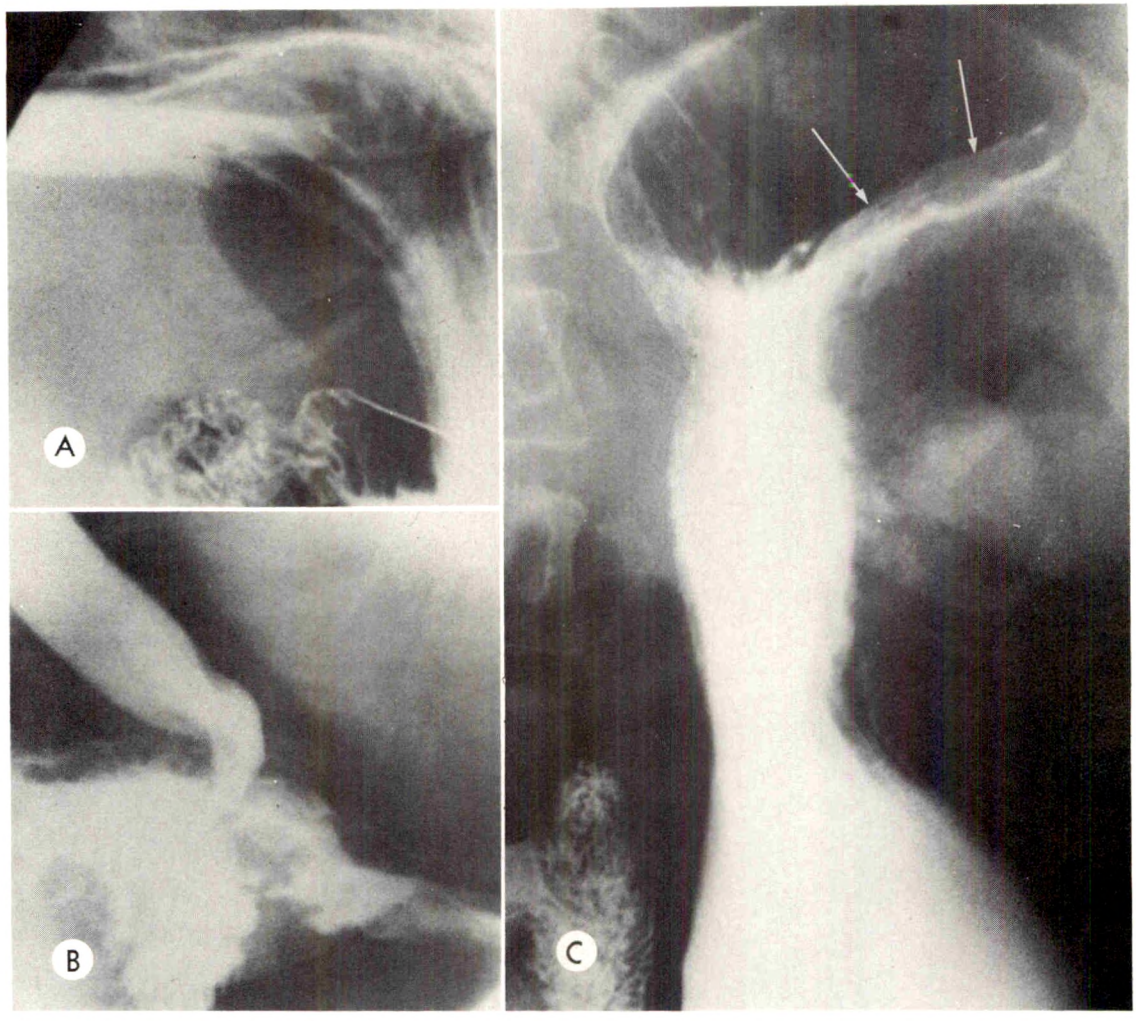


Fig. 4. Nonpersistent cascade.

(*A* and *B*) Spot roentgenograms from the initial stages of an upper gastrointestinal series demonstrate a cascade configuration with obvious posterior loculation of the fundus. (*C*) A large amount of barium opens the stomach. The cascade configuration disappears. Indentation by the splenic flexure of the colon on the stomach is seen (arrow).

body of the stomach with the anterior and posterior walls in the same coronal plane as the anterior and posterior walls of the body of the stomach. Ordinarily, there is no clear demarcation between the upper part of the body and the fundus. All walls demonstrate a smooth, essentially straight, continuum. In some cases, however, the fundus is a posterior loculus either directly behind or slightly to the right or left. A "ridge" is then apparent posteriorly which produces a radiologically evident demarcation between the fundus and body of the stomach (Fig. 1, *A–F*). If this "ridge" is not horizontal, but turns upward at its anterior end, the fundal loculus then lies inferiorly relative to the proximal portion of the body of the stomach. The fundus, in this situation, still lies in its usual position relative to the structures of the left upper quadrant but the proximal portion of the body of the stomach is in an abnormally anterior and superior position. When this type of stomach is filled with barium (in the erect position), static roentgenograms may demonstrate a separate fluid level

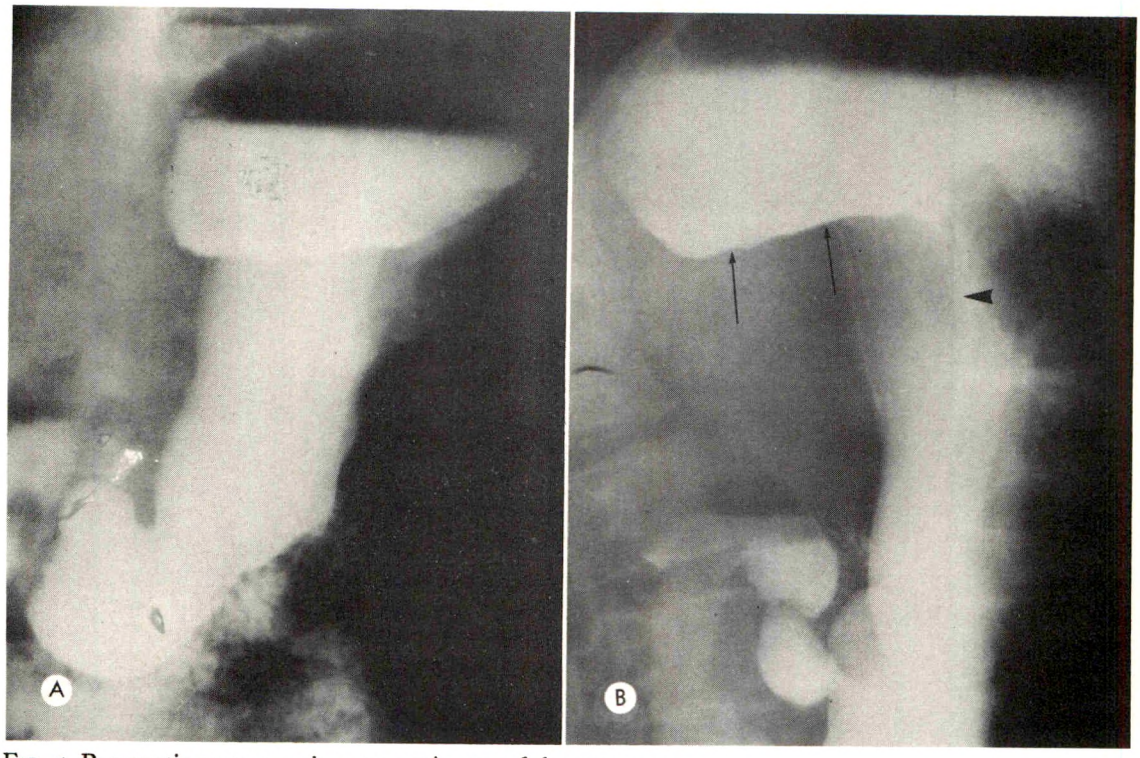


Fig. 5. Pancreatic cyst secondary to carcinoma of the pancreas.
(*A*) There is a persistent cascade in the erect position with no obvious explanation. (*B*) The right anterior oblique roentgenogram demonstrates a mass behind the stomach producing a "ridge" (arrows). The uninvolved left lateral margin of the body of the stomach (arrowhead) produces a double contour. The gas distended splenic flexure is seen through the barium laterally and is unrelated to the cascade.

confined to the fundus. At fluoroscopy, barium first fills the dependent, posterior fundus to the highest level of the "ridge" and then spills or "cascades" into the body and antrum. It is the latter phenomenon which has been classically used in the roentgen literature to define the cascade stomach.[6,7] Partial organoaxial volvulus of the stomach may, at times, simulate the appearance of a marked cascade configuration when the stomach lies in a transverse plane. The upward rotation of the greater curvature characteristic of volvulus and the low position of the cardia clearly differentiate this condition from the true cascade stomach.[1]

In this paper, we would like to use the term "cascade stomach" in a somewhat more precise fashion. In the erect position, the presence of a posterior "ridge" which delineates a boundary between the fundus and body of the stomach is used to define the presence of a cascade configuration. This definition would also include the classic description of the cascade deformity. We should, also, like to point out that the nonpathologic cascade configuration of the stomach is not as common as is generally believed. Many "cascade" stomachs are the result of intrinsic or extrinsic gastric lesions. Therefore, the recognition of this deformity in the erect position at the onset of a barium series should alert the radiologist to the possibility that an organic lesion may be present.

NORMAL ROENTGENOGRAPHIC FINDINGS

The cascade configuration of the stomach which is seen in the absence of significant pathologic abnormality is most often associated with a gas distended distal trans-

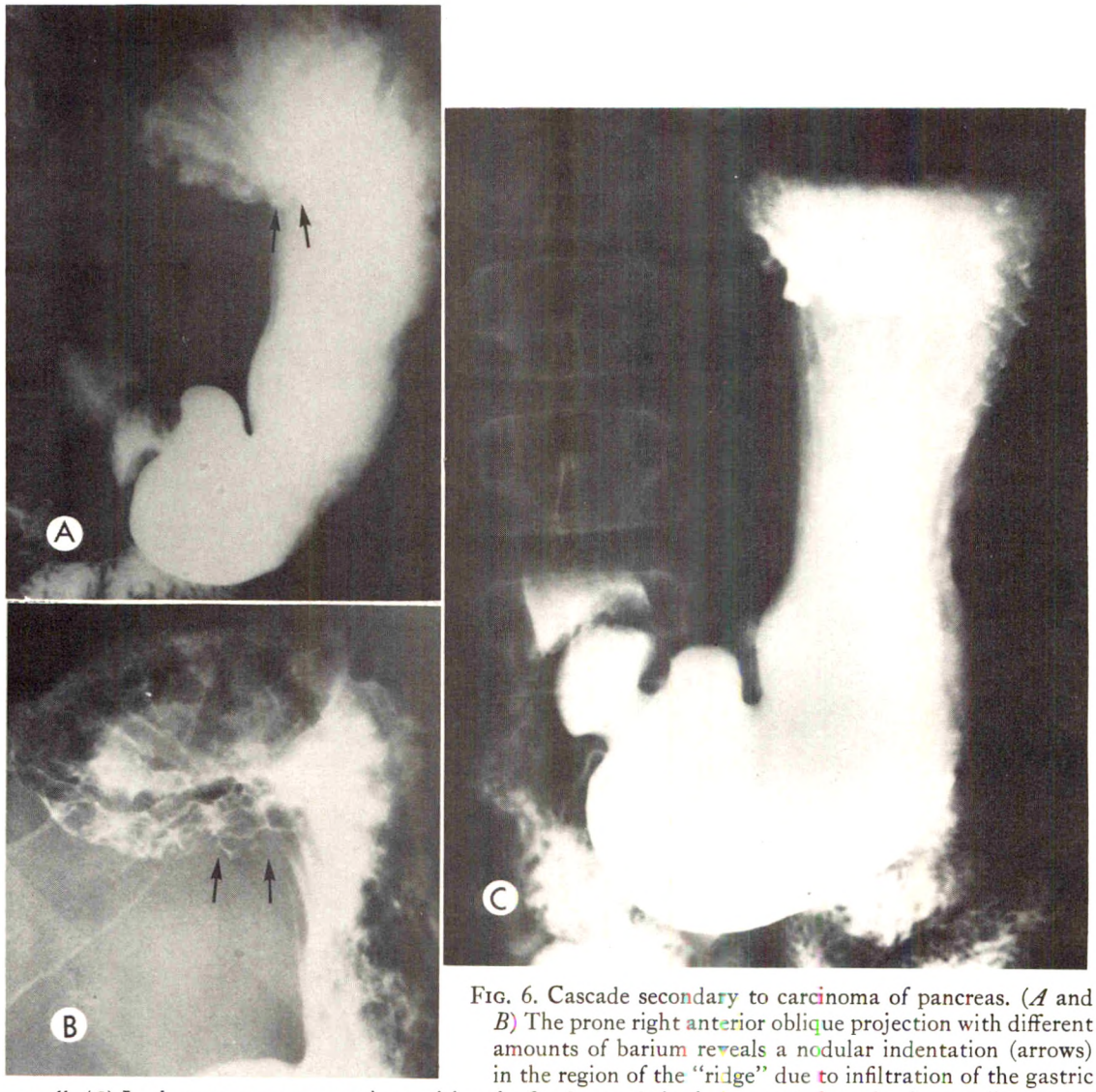


Fig. 6. Cascade secondary to carcinoma of pancreas. (*A* and *B*) The prone right anterior oblique projection with different amounts of barium reveals a nodular indentation (arrows) in the region of the "ridge" due to infiltration of the gastric wall. (*C*) In the erect posteroanterior position the fixed cascade is obvious and the only abnormality.

verse colon or proximal limb of the splenic flexure (Fig. 2, *A* and *B*; and 3, *A* and *B*). In these cases, the gas distended colon is located behind and somewhat to the left of the body of the stomach and displaces the body anteriorly thus creating the cascade configuration. The "ridge" formed at the junction of the fundal loculus and the body is sharp, well defined and either straight or convex toward the fundus. In the erect frontal projection, a double loculus created by overlapping of the fundus and body is evident. In the recumbent position, the junctional area between the body of the stomach and the more proximal fundal region is not clearly defined by barium and there are no sudden or sharp changes in the caliber, contour or direction of the stomach at any level.

Radiologists are well acquainted with the difficulties involved in the adequate examination of the fundus in all patients. This difficulty is enhanced by the presence of the cascade configuration. Various maneuvers have been designed to perform a more adequate examination of the area.

These include: oblique projections in the erect position, both right and left, and lateral views; filling the fundus of the stomach with barium, the patient supine, and then tilting the patient toward the erect position, spotting the fundus as the barium spills out of it; turning the patient, in the supine position, towards the left and the right while conducting a similar maneuver; and cross table lateral views. The left anterior oblique erect roentgenogram of the stomach is perhaps better suited to delineate the posterior wall of the upper portion of the body of the stomach because, in this position, the fundus is less likely to obscure the region.

At times, although a cascade configuration is noted with the first few swallows of barium in the erect position, it disappears with further filling of the stomach (Fig. 4, *A–C*). Apparently, the weight of the intraluminal fluid in the antrum is such that the stomach is opened up and presents as a single chamber. A single barium air level is then seen.

ROENTGEN-PATHOLOGIC FINDINGS

We have been impressed by the fact that true physiological or normal "cascade," using the above definition, is by no means as common as is ordinarily thought. Patients with a cascade stomach have demonstrated a variety of lesions both intrinsic and extrinsic primarily related to the posterior wall of the stomach. Cascading secondary to anterior growth of a retrogastric mass is a simple manifestation and easy to understand (Fig. 5, *A* and *B*). In most instances, this is the result of a mass in the body and/or tail of the pancreas either

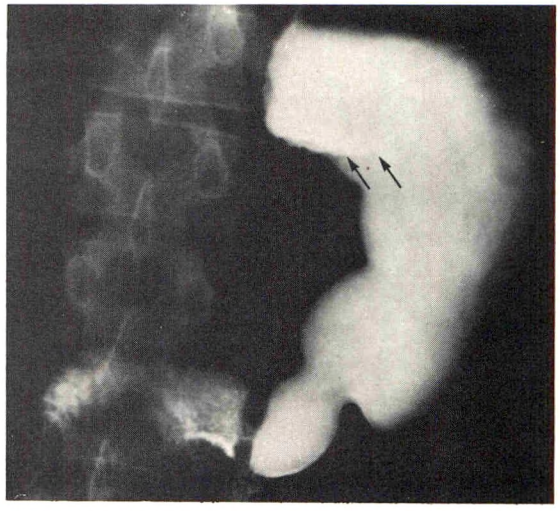


Fig. 8. Cascade deformity secondary to postoperative changes: splenectomy. Persistent cascade (arrows) in the erect position secondary to lateral and superior displacement and rotation of the body of the stomach following splenectomy.

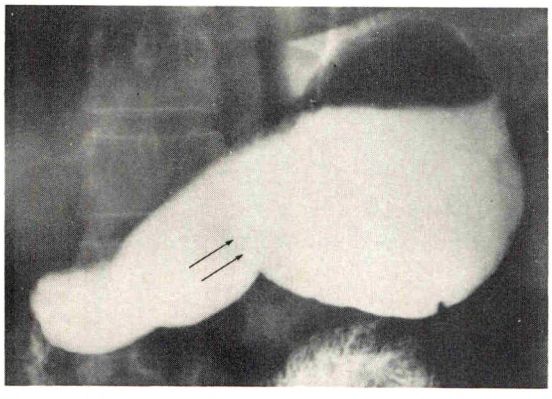


Fig. 7. Cascade deformity secondary to postoperative adhesions: cholecystectomy. Persistent cascade (arrows) in the erect position post-cholecystectomy is most likely secondary to rotation of the body of the stomach anteriorly, superiorly and to the right due to adhesions forming in the region of the lesser omentum.

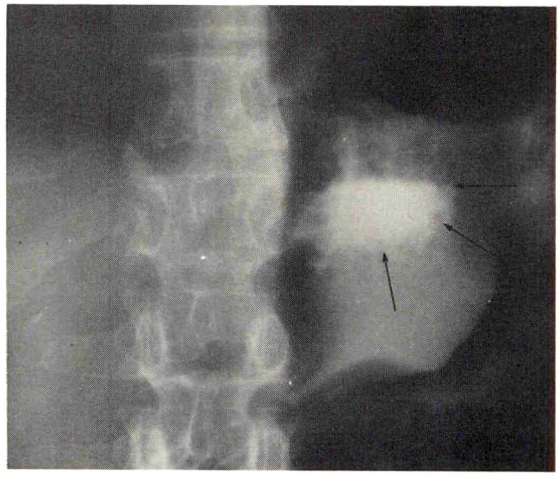


Fig. 9. Cascade deformity secondary to eventration of the left hemidiaphragm. Eventration of the left hemidiaphragm documented for at least 8 years with no change in that period of time. A persistent cascade deformity is noted (arrows).

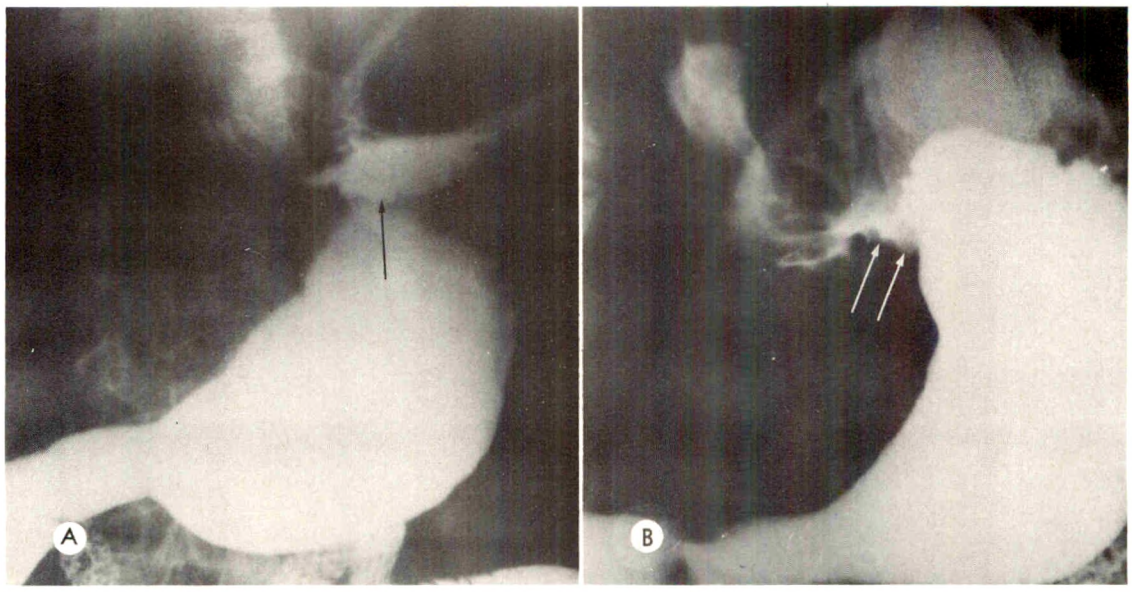
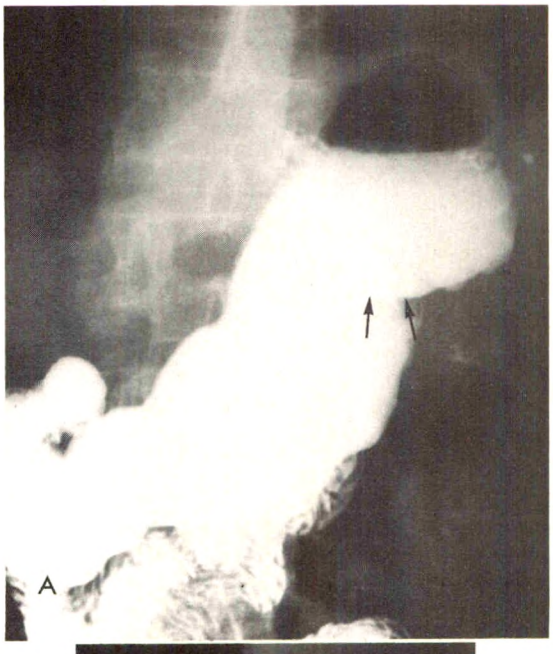
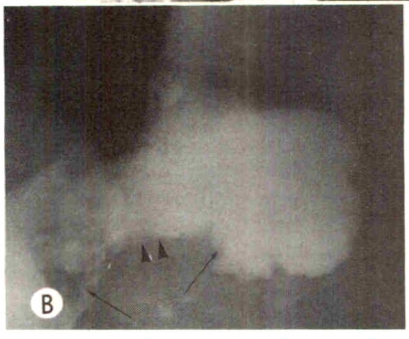


FIG. 10. Cascade secondary to gastric ulcer.

(*A*) A persistent cascade deformity is noted in the erect position (arrow). In addition, a nondescript narrowing of the upper portion of the body of the stomach and the fundus is evident. (*B*) The prone right anterior oblique roentgenogram demonstrates an ulcerated area in the region of the "ridge" (arrows). This was proved to be a benign ulcer.





malignant neoplasm or the result of pancreatitis and pseudo-cyst formation. A tumor of the adrenal may produce a similar configuration. If the mass infiltrates the posterior wall of the stomach as well, additional findings include shortening, irregularity and nodularity of the "ridge" seen in the erect position and abrupt changes in the caliber, contour or direction of the upper portion of the stomach seen in the recumbent position (Fig. 6, *A–C*). Occasionally, even soft tissue intrusion into the lumen of the stomach may be observed.

Cascading may also occur secondary to other extrinsic factors, *e.g.*, adhesions with shortening of the ligamentous attachments of the stomach after abdominal surgery such as cholecystectomy (Fig. 7). After splenectomy, a somewhat similar

FIG. 11. Cascade secondary to carcinoma of the stomach.

(*A*) Persistent cascade in the erect position is manifested by a laterally directed pouch (arrows). There is no obvious mass. (*B*) The right posterior oblique roentgenogram in the supine position delineates a large ulcerated tumor (arrowheads) which is circumferential in the region of the "ridge" (arrows). Extrinsic extension of tumor is likely.

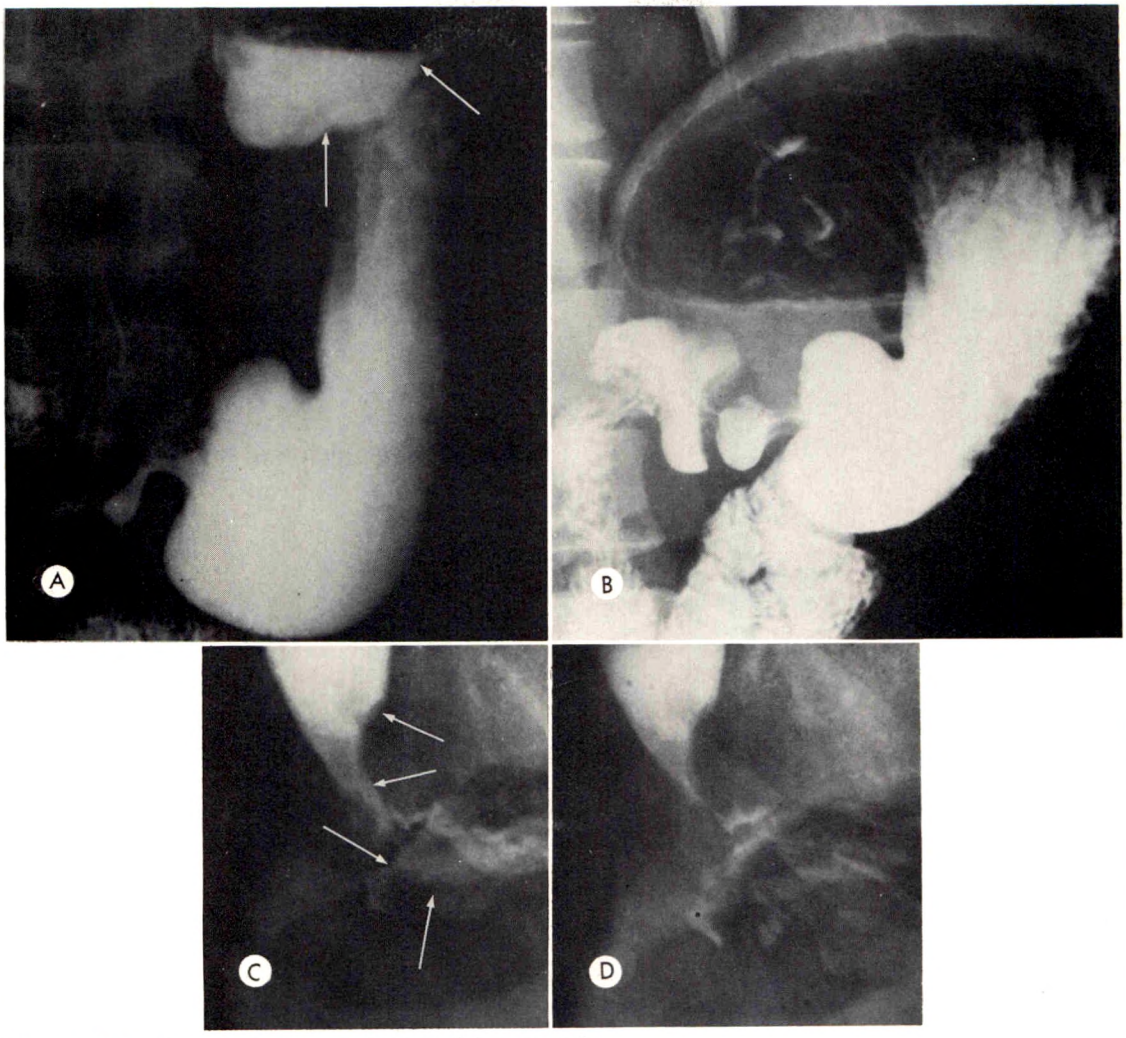


Fig. 12. Cascade secondary to carcinoma of the stomach.

(*A*) A persistent cascade is seen in the erect position (arrows). At the cardia, a lobulated soft tissue mass is evident through the gas in the fundus. (*B*) The tumor in the fundus is delineated by irregular, curvilinear collections of barium with distorted mucosa between. (*C* and *D*) A nodular defect of the distal esophagus (upper arrows) and an irregular ulcerated area (lower arrows) in the fundus are seen. At operation, the tumor extended through the gastric wall posteriorly and was fixed to the posterior peritoneal wall.

cascade deformity in the opposite direction may occur as a result of the body of the stomach occupying the additional space posteriorly and laterally (Fig. 8). Eventration of the left hemidiaphragm produces a cascade configuration by elevation of the body of the stomach with maintenance of the normal position of the cardia (Fig. 9).

Intrinsic disease of the stomach may also result in the cascade configuration. Chronic benign peptic ulcer may occur near the junction of the fundus and the body of the stomach on the posterior wall either medially or laterally (Fig. 10, *A* and *B*). These ulcers frequently are associated with considerable shortening of the wall about the ulcer either as a result of spasm or fibrosis.[5] In addition, adhesions to adjacent organs as a result of posterior penetration of the ulcer through the gastric wall with persistent distensibility of the anterior gastric wall contribute to the cascade configuration. Intrinsic gastric carcinoma may also be associated with the presence of a cascade

deformity (Fig. 11, *A* and *B*; and 12, *A–D*). A prime factor in the development of a cascade of this type is most likely fixation of the posterior gastric wall to the posterior parietes by tumor extension. Elkeles[2] describes several cases of carcinoma of the fundus, intrinsic and extrinsic, in which a "pouch-like" protrusion at the lower posteromedial border of the fundus was produced, in effect, a cascade configuration.

CONCLUSION

The examination of the gastric fundus is usually the most difficult part of a complete examination of the stomach. It is important to realize that examination of this region in the presence of a cascade configuration requires even greater attention, despite the greater difficulty encountered.

In the erect position, a persistent cascade configuration, as defined by the presence of a posterior "ridge" delimiting fundus from body, suggests the possibility of a high posterior gastric or retrogastric lesion.

A cascade stomach should not be considered physiologic or within normal limits until a detailed examination of the area is satisfactorily performed.

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TABLE II

INCIDENCE OF SURVIVAL AMONG 53 PATIENTS WITH PERFORATION LISTED BY LOCATION AND CONTRIBUTORY FACTORS

Site:	Esoph-agus	Stomach	Duode-num	Small Intestine	Colon	No Site Found	Total
No. of Patients	3	12	3	16	14	5	53
Metabolic							
Prematurity	1/2	6/9		2/7	0/1	0/3	9/22
Respiratory distress				1/2		0/2	1/4
Cystic fibrosis			0/1	0/1			0/2
Hypoglycemia				0/1			0/1
Jaundice		1/2		0/2	1/1		2/5
Aplastic anemia				0/1			0/1
Genetic							
Twin						0/1	0/1
Triplet		1/1					1/1
Absent radius	0/1						0/1
Inflammatory							
Sepsis		2/2	0/1				2/3
Mediastinitis	0/1						0/1
Gastritis		1/1					1/1
Appendicitis					0/1		0/1
Abscess					1/1		1/1
Enterocolitis				1/3			1/3
Peritonitis				0/1		1/1	1/2
Mechanical							
Atresia	0/1			2/3			2/4
Anal malformation					1/2		1/2
Absent muscle layer		0/1					0/1
Duplication	1/1	0/1	0/1				1/3
Eventration, diaphragm		1/1					1/1
Malrotation				0/3	0/1		0/4
Meconium ileus				0/2			0/2
Meconium peritonitis			0/1	3/4			3/5
Postoperative							
Atresia				1/1	1/1	0/1	2/3
T-E fistula	0/1						0/1
Vascular malformation				1/1			1/1
Foreign body	1/1						1/1
Meconium ileus				0/1			0/1
Intussusception					1/1		1/1
Appendicostomy					0/1		0/1
Colostomy					1/2		1/2
Transfusion for Rh incompatibility					1/1		1/1
Barium Enema							
Malrotation				0/1	0/1		0/2
Hypoplasia of abdominal wall					0/1		0/1
Balloon blowout					1/1		1/1
Unexplained		3/4			1/2		4/6

open safety pin from the esophagus; one communicating with a pulmonary abscess complicating a cystic teratoma; and one a late sequela which developed 5 months after surgical ligation of a tracheo-esophageal fistula associated with esophageal atresia. The first 2 of these survived, but the last-named patient developed bilateral pleural fluid collections and expired without warning during thoracentesis. The fluid withdrawn proved to be chyle, with a high amylase content. The gap between segments of the esophagus had been too wide to afford direct anastomosis, and the patient was fed successfully by gastrostomy pending the time that he could have an esophageal bypass carried out. The boy also had bilateral absence of radii and thumbs. At autopsy there was an acute mediastinitis which appeared to be the result of a perforation of the distal (blind) esophageal segment.

STOMACH

Twelve perforations developed in the stomach. The 5 in Series A *all* occurred in the first week of life, and 6 of the 7 in Series B during the first 10 days postpartum. The one gastric perforation in an older infant occurred at 7 months at the site of a duplication on the greater curvature which ulcerated and perforated into the lesser sac. The child survived.

Nine of the 12 patients with gastric perforations were born prematurely. Those whose defects were discovered and treated promptly were the most likely to recover, and 6 of the 9 survived. One of these was one of triplets. Her abdomen became distended on her second day, and although meconium was passed she did not stool. On the fifth day of life a barium enema study was carried out, which was interpreted as showing a normal colon but a small bowel obstruction. On her sixth day she was transferred to Babies and Childrens Hospital critically ill (Fig. 4, *A* and *B*). Following aspiration of 65 cc. air from the abdomen, a laparotomy was carried out which revealed a perforation of the cardia posteriorly into the lesser sac. Following repair, the child recovered.

Our best salvage rate in the management of gastrointestinal perforations was in those involving the stomach. Nine of the 12 patients recovered and are well.

DUODENUM

Three patients perforated their duodenums: 2 in the newborn period; and 1 at 3 months. The latter was hospitalized elsewhere for dehydration and malnutrition, and the parents were told she had a "nervous brain." Upon transfer to Babies and Childrens Hospital she was found to have a large quantity of free air in the abdomen (Fig. 5, *A* and *B*). At laparotomy an ulcer was discovered in the first part of the duodenum and was repaired. Eleven days postoperatively she died of aspiration pneumonia. Autopsy (in 1952) revealed a heretofore unsuspected fibrocystic disease of the pancreas.

The 2 newborn patients perforated at sites of a duplication cyst and meconium peritonitis. All 3 patients with duodenal perforations succumbed. All duodenal perforations took place in Series A.

SMALL INTESTINE

The greatest incidence of perforation of the gastrointestinal tract took place in that part which is the longest: 16 in the small intestine. Those most successfully treated were the ones with atresia and/or meconium peritonitis which were diagnosed early.

Neonatal necrotizing enterocolitis is an etiology which we have encountered only in the past 3 years—approximately the period of time that early feeding and assisted ventilation have been instituted to prolong the survivals of premature infants who otherwise would probably have succumbed from immaturity and respiratory distress syndrome before they became victims of the complex events that lead to perforation.[2] During these 3 years we have had about 20 sporadic cases of enterocolitis in our newborn nursery. The intestine has

perforated in 3 of these, among whom 1 has survived (Fig. 6, *A* and *B*).

Six of the 16 patients with perforation of jejunum and ileum survived.

COLON

Fourteen perforations were found in the colon. Eight patients survived. Half that number experienced perforation *in the hospital* following surgery or other manipulative procedure, so their difficulties received early recognition and treatment. An additional 4 cases resulted from manipulative procedures by radiologists, *viz.* barium enemas. Three times this occurred in our department and once in a neighboring city (Case IV in Ref. 6). Our most recent such experience took place in 1965 in a 1 week old infant being examined for a 12 hour history of bloody stools. The patient expelled the Foley catheter which was inserted into the rectum for the enema. It was reinserted, but upon passage of contrast material the barium flowed into the peritoneal cavity (Fig. 7*A*). At surgery immediately thereafter a 3 cm. posterior-wall sigmoid laceration was found and closed. The peritoneal cavity was lavaged, but considerable barium remained in it. Six months later the patient returned with a small bowel obstruction (Fig. 7*B*), which laparotomy showed to be due to adhesions compressing the jejunum. Particulate barium was, of course, found on the peritoneal surface, and a biopsy of one such focus was reported by the pathologist as a "barium granuloma."

NO SITE FOUND

Five cases remain which upon roentgenographic examination demonstrated indisputable evidence of free intraperitoneal air, but whose surgical explorations failed to identify a source of perforation. One of the 5 had an *E. coli* peritonitis, and survived. Three others were premature infants, 2 with severe respiratory distress syndrome, and all succumbed. One of the latter was a small infant weighing 3 lb. 5 oz. at birth who was transferred 1 hour later to our hospital for ventilatory assistance with oxygen by mask and bag

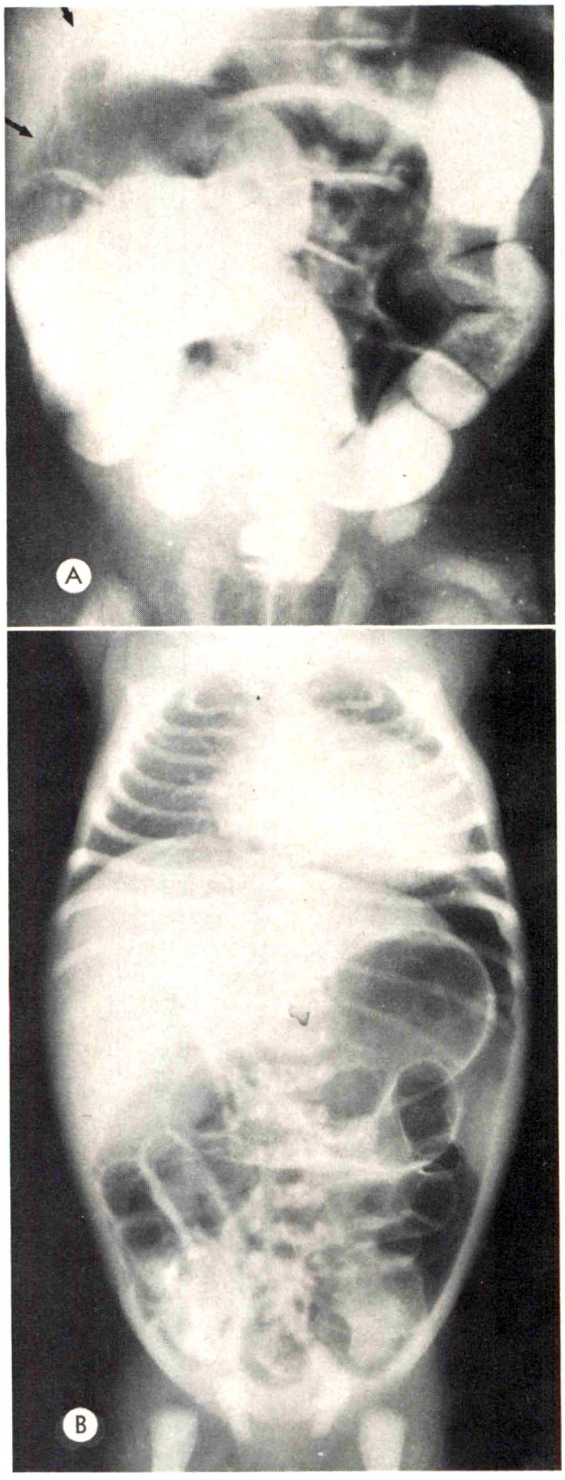

FIG. 4. (*A*) A barium enema examination on Day 5 was considered to have demonstrated a normal colon. Free intraperitoneal air can also be seen in the interstices of the abdomen (arrows). (*B*) Upon arrival at Babies and Childrens Hospital on Day 6, the baby's gastrointestinal tract is seen to be distended with gas, as is the peritoneal cavity.

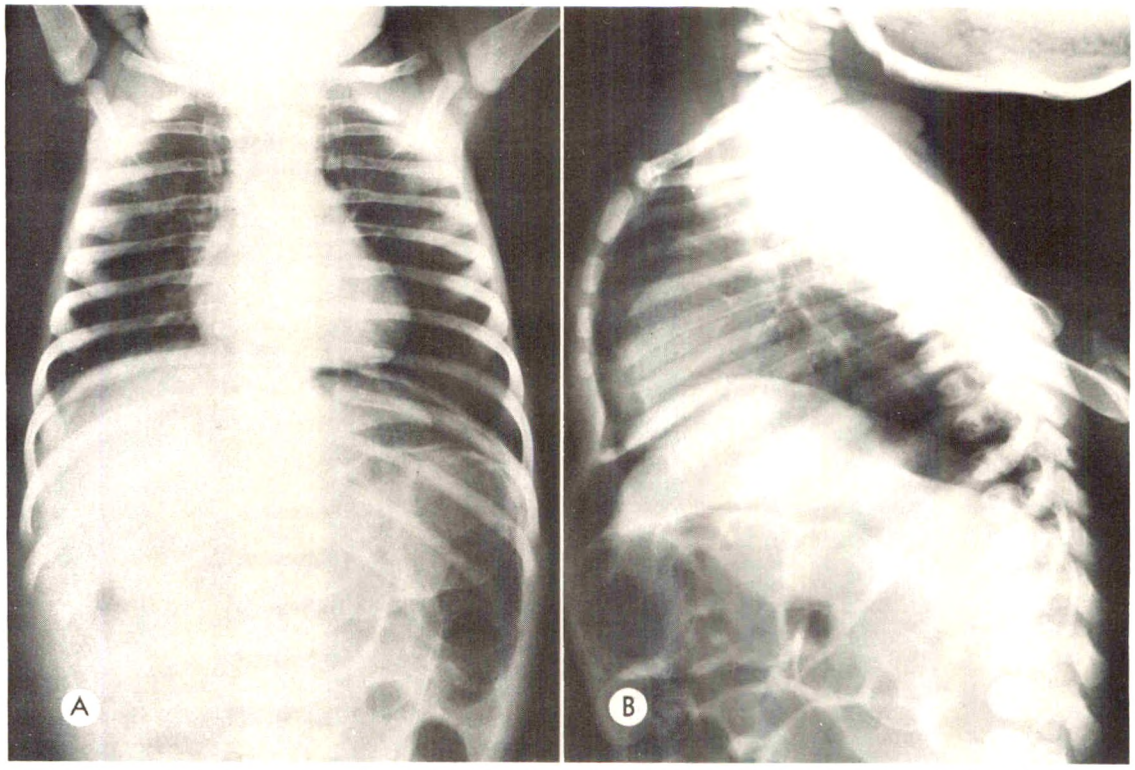

FIG. 5. (*A* and *B*) Chest and abdomen of a 3 month old malnourished female upon arrival at Babies and Childrens Hospital. Free abdominal air can be seen on recumbent roentgenograms. At laparotomy a perforation was found at the site of a duodenal ulcer.

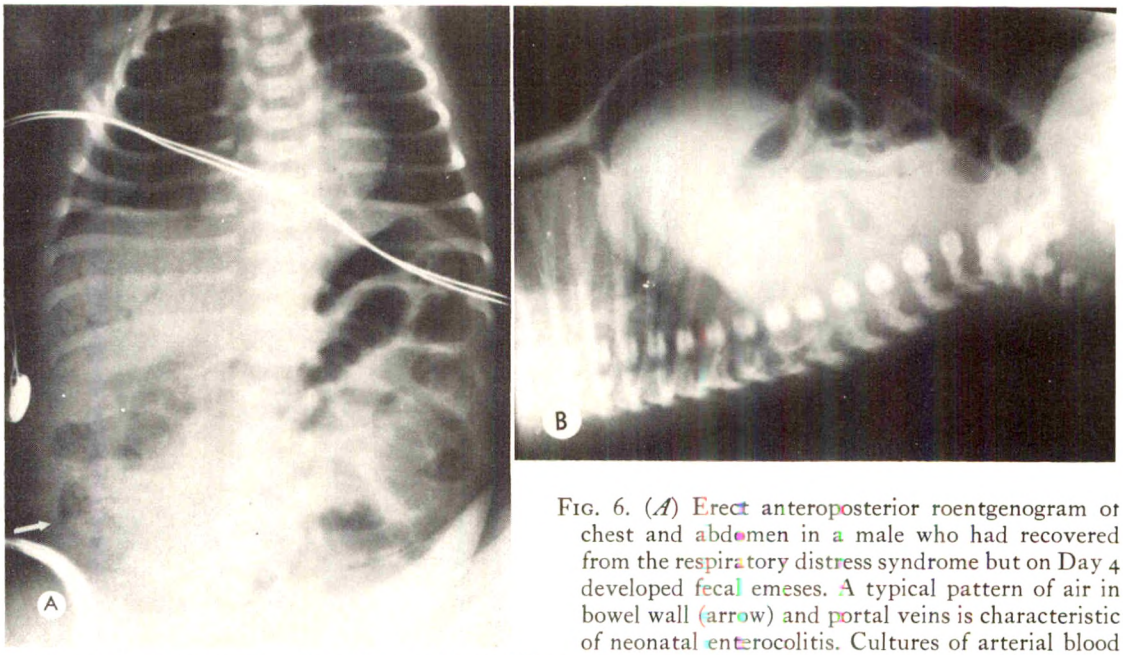

FIG. 6. (*A*) Erect anteroposterior roentgenogram of chest and abdomen in a male who had recovered from the respiratory distress syndrome but on Day 4 developed fecal emeses. A typical pattern of air in bowel wall (arrow) and portal veins is characteristic of neonatal enterocolitis. Cultures of arterial blood and gastric content grew *Enterobacter cloacae*. The patient was treated with intravenous antibiotics and steroids, and his clinical state improved. On Day 9, however, his abdomen became distended. (*B*) A cross-table lateral roentgenogram revealed free intraperitoneal air. At laparotomy the source of the air was found to be a rent in the ileum, which was plicated. The patient recovered and was discharged in good health at 1 month of age.

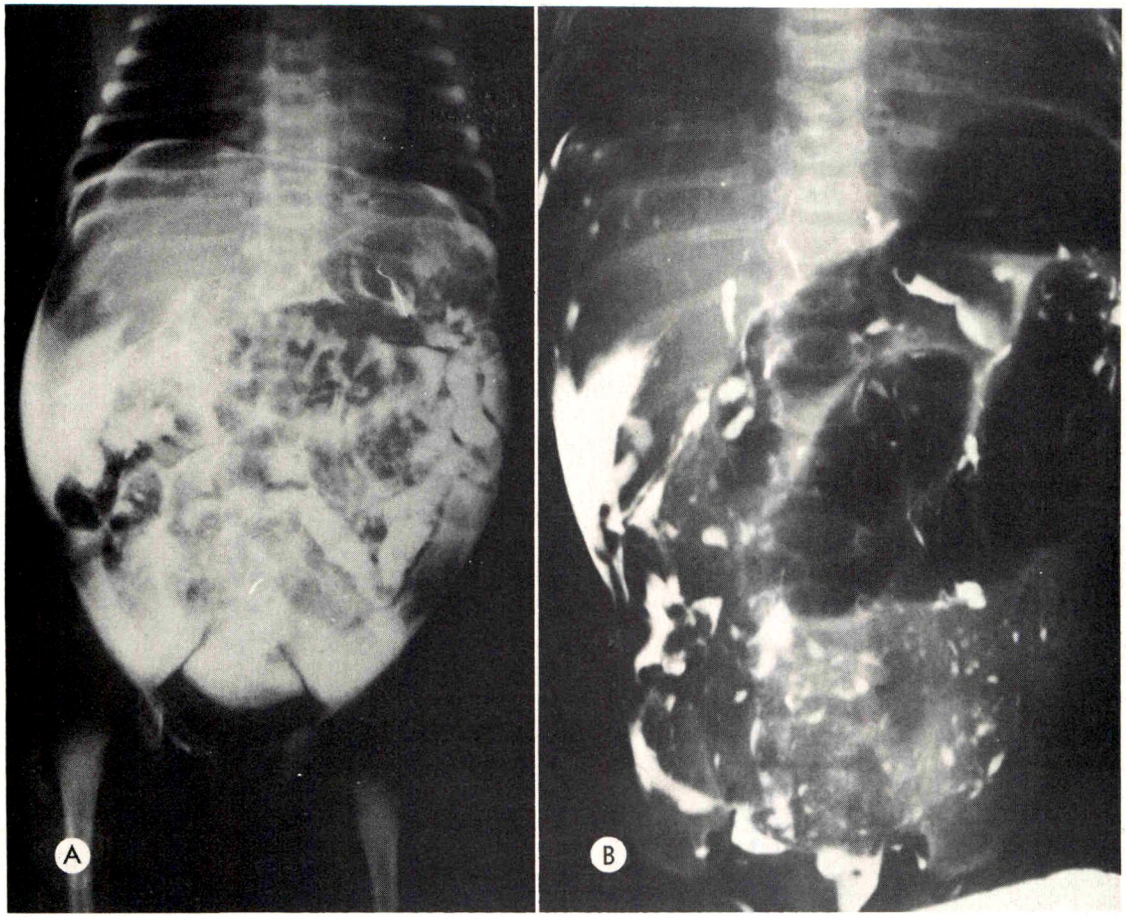

Fig. 7. (*A*) A 1 week old female was given a barium enema because of bloody stools. The barium flowed freely into the peritoneal cavity. At surgery a large rent was found in the sigmoid colon at the site of inflation of a Foley balloon used in administering the enema. (*B*) The child at 6 months of age is shown on an erect roentgenogram to have the picture of small bowel obstruction. Laparotomy disclosed the cause to be due to peritoneal adhesions. The roentgenogram demonstrates the barium residue from the perforation which took place at the time of the previous barium enema examination in *A*.

(Fig. 8*A*). The child responded well at first, but at 33 hours of age suddenly became distended with a rigid abdomen (Fig. 8*B*) and promptly expired. Autopsy revealed ulcerations of stomach and duodenum but no site of perforation. There were extensive hyaline membranes, and the supposition was that the pneumoperitoneum arose not from intestinal perforation but from transdiaphragmatic dissection of air from a bronchus which may have been ruptured by the bag-breathing.[1,3,4] In the absence of pneumomediastinum, pneumothorax, or interstitial pulmonary emphysema on the roentgenogram, there is no way to substantiate this supposition.

SUMMARY

Over a 22 year period, 53 infants under 1 year of age suffered gastrointestinal perforations. Seventy-two per cent of these took place during the first week of life.

Predisposing factors have been found to range widely through the following general categories: metabolic, genetic, inflammatory, mechanical, and unexplained. Twenty-two of the babies were born prematurely.

Sixteen perforations were iatrogenic. Of these, 11 followed a variety of surgical procedures, 1 developed subsequent to transfusion, and 4 resulted during or after barium enema examinations.

The anatomic distribution showed the

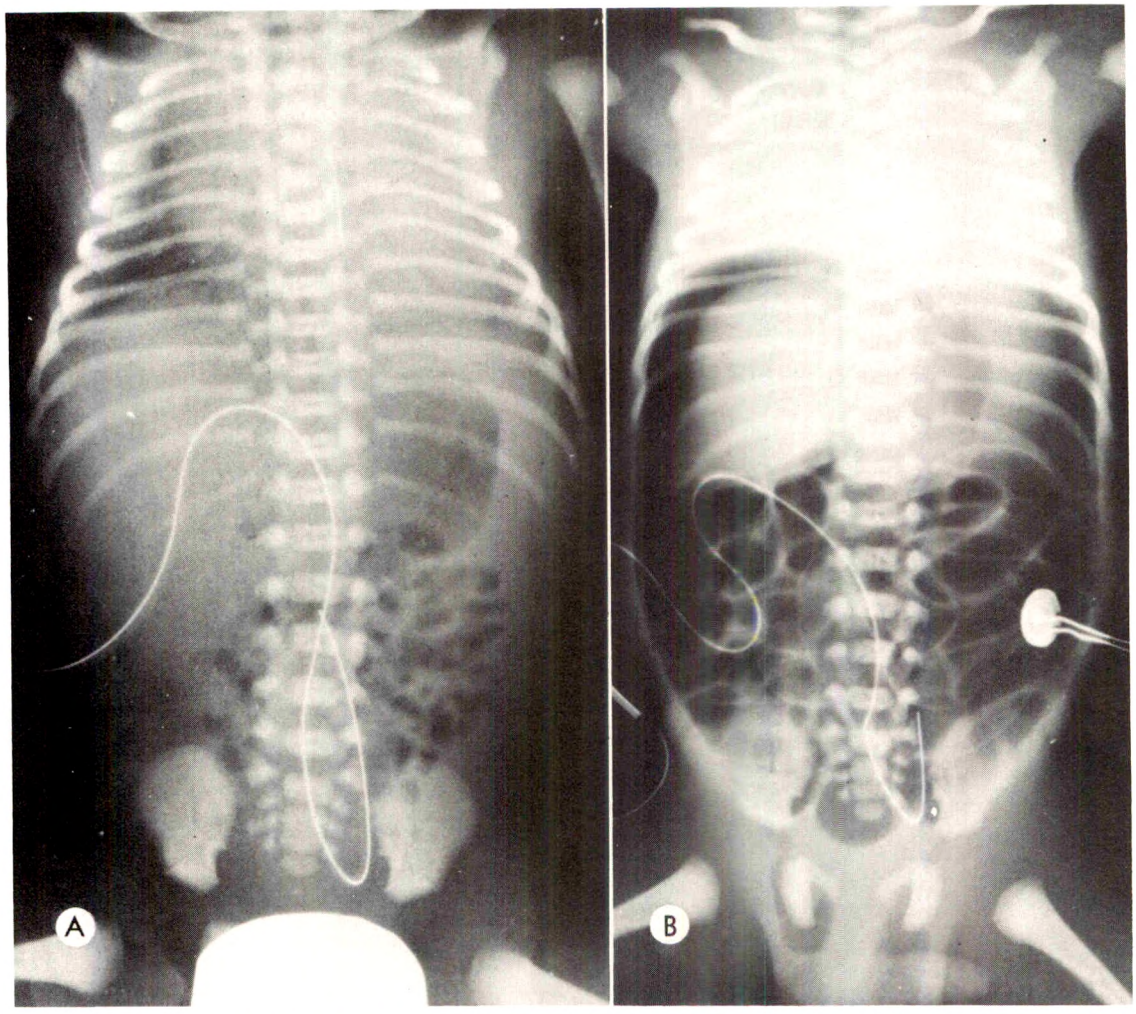

Fig. 8. (*A*) Chest roentgenogram of a 1,500 gm. female at 1 hr. 15 min. shows evidence of early respiratory distress syndrome. (*B*) At 33 hours the child's condition suddenly deteriorated. The roentgenogram shows the lungs virtually completely opacified, and the abdomen (including the processus vaginales) distended with free air. The child could not be revived. At autopsy no site of perforation could be found.

stomach, the small intestine, and the colon each accounting for between 23 and 30 per cent of the total. Perforations of esophagus and duodenum were much less frequent, 3 each. In 5 patients a site of perforation was not identified.

Twenty-six of the patients survived—an incidence of 49 per cent. The highest survival was in stomach perforations, 9 out of 12 (75 per cent). None of the 3 infants with duodenal perforation lived. Constant vigilance is required, of clinician and radiologist, to be on the lookout for the earliest signs of gastrointestinal perforation. The patient's best hope for survival lies in prompt diagnosis and treatment.

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INTESTINAL STRICTURES IN THE NEONATE*

A COMPLICATION OF ISCHEMIC BOWEL DISEASE

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OVER the past decade ischemic bowel disease (IBD) has become an increasingly well recognized clinical entity in the adult patient.[21,27,28] However, until recently very little had been written about the subject in the neonate. Although there is a prior knowledge that vascular accidents can occur in the pediatric age group, all too often the possibility fails to be considered in acute problems of the gastrointestinal tract of the infant. Concomitantly, stricture formation is a well documented late complication of IBD in the adult, but the radiologic literature concerning this problem in the neonate is sparce.

It is the purpose of this paper to discuss 4 patients with IBD due to varying etiologies, who later developed gastrointestinal strictures.

Classically, the underlying factors responsible for IBD in the adult have been divided into occlusive and nonocclusive categories.[27] Although the etiologic mechanisms may be quite different in the neonate, this classification of occlusive and nonocclusive ischemia is still applicable (Table 1).

OCCLUSIVE ISCHEMIC BOWEL DISEASE-MECHANICAL OCCLUSION

Intussusception of the newborn is a relatively rare phenomenon,[29] but it is capable of creating an ischemic bowel segment by a mechanical occlusion of the vessels. A 3 day old infant presented with bilious vomiting and blood per rectum. An iliocolonic intussusception was diagnosed by barium enema (Fig. 1*A*) and then surgically reduced. Five months later, because of failure to thrive, recurrent vomiting, and abdominal distention, another barium enema study was performed (Fig. 1*B*); it demonstrated a localized narrowing of the proximal left colon. Re-exploration proved that the narrowed segment was due to ischemic stricture. This narrowing had not been present at the original surgery. Apparently, the degree of ischemia to the bowel wall from the intussusception was not sufficient to have caused a full thickness infarction with subsequent perforation. However, restoration of the blood supply following reduction of the intussusception did allow healing of this segment, but with associated fibrosis and stricture. The stenotic area in the colon was resected, and an end-to-end anastomosis was performed.

Trauma represents another etiologic mechanism in the pathogenesis of IBD. In some instances the precipitating event may be iatrogenic. A newborn male was found to have a high imperforate anus for which a "pull through" operation was performed on the first day of life. It is unusual to perform this type of surgery in a neonate; considerable manipulation of the distal colon, and its blood supply, is required. At 3 weeks of age the patient was referred to Duke Hospital with a partial intestinal obstruction. A contrast study of the colon (Fig. 2*A*) demonstrated a stricture in the sigmoid colon. A carefully selected dietary regimen permitted the child to grow, but at 1 year of age severe constipation led to a repeat barium enema examination. This study demonstrated a persistence of the narrowing in the sigmoid colon; this lesion was felt to represent an ischemic stricture secondary to inadvertent

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Table I

CAUSES OF ISCHEMIC BOWEL DISEASE IN THE NEONATE

I. *Occlusive*
  A. Primarily arterial involvement
    1. Mechanical arterial occlusion
      a. intussusception
      b. trauma-postoperative
      c. mid-gut volvulus
    2. Thromboembolic phenomena
      a. emboli originating in placental or umbilical veins[9]
      b. postcardiac surgery mural thrombi[7]
      c. umbilical artery catheterization[10,20,26]
    3. Primarily venous involvement
      1. perforation following exchange transfusion[2,4,16,24]
      2. dehydration[7]
      2. sepsis[7]
      4. postoperative-trauma[5,18]
II. *Nonocclusive*
  A. Necrotizing enterocolitis[14,25]

interruption of the blood supply of the colon at the time of surgery. The patient is currently being given a trial of medical management.

OCCLUSIVE ISCHEMIC BOWEL DISEASE-THROMBOEMBOLIC PHENOMENA

Embolization from thrombi in the venous channels of the placenta or from thrombi in the umbilical vein has been cited as a cause of gastrointestinal ischemia.[9] An embolus originating in either of these locations may travel through the ductus venosus and ductus arteriosus (or foramen ovale) to reach the splanchnic circulation. Such an embolus could either be spon-

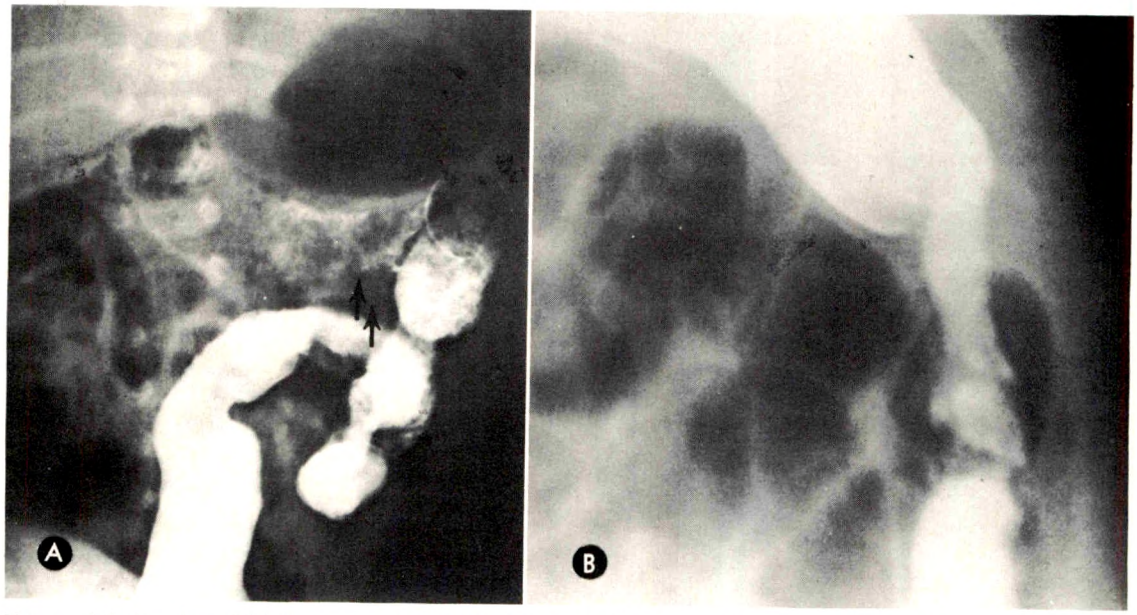

Fig. 1. (*A*) A 3 day old infant presented with bilious vomiting and blood per rectum. Top arrow points to filling defect caused by an ileocolic intussusception. Bottom arrow marks the wall of the distal transverse colon. (*B*) Five months later, symptoms of a partial intestinal obstruction prompted another barium enema examination. A stricture of the proximal left colon was demonstrated.

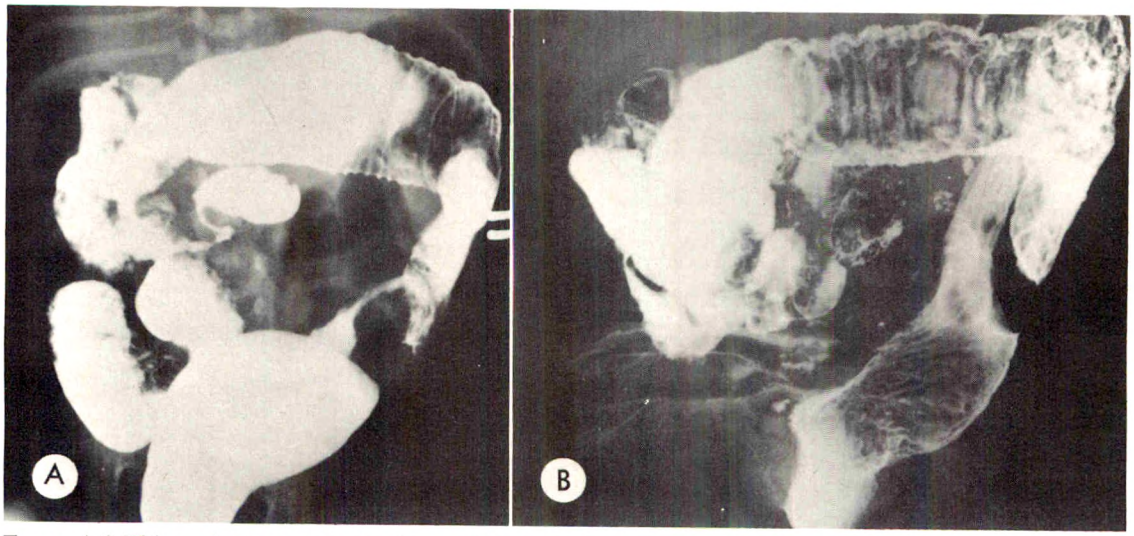

Fig. 2. (*A*) This patient was noted to have a high imperforate anus at birth; a "pull through" operation was performed on the first day of life. Three weeks later the patient was referred with symptoms of a large bowel obstruction. Barium enema examination revealed an ischemic stricture in the sigmoid colon. (*B*) A repeat barium enema study 1 year later shows persistence of the stenosis.

taneous, or it could be iatrogenic, following umbilical vein catheterization. Occlusion of a mesenteric vessel by the embolus would lead to varying degrees of bowel ischemia. With only moderate ischemia and good collateral flow, total necrosis of the bowel wall might not occur, but subsequent healing of the wall by cicatrix would lead to stricture formation.

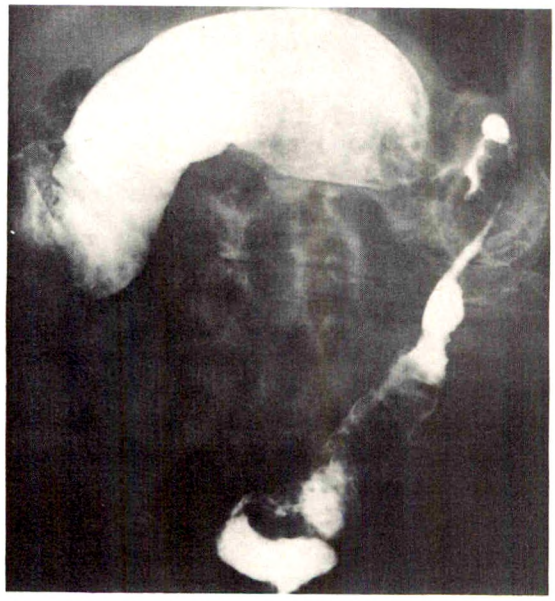

Fig. 3. Barium enema study reveals a "congenital" colonic stenosis in this 2 day old neonate. A knot in the umbilical cord caused venous congestion and thrombus formation in the umbilical vein. Emboli from this source may well have caused a mesenteric vascular accident *in utero*.

A full term infant developed abdominal distention after birth, and on the second day of life a barium enema study revealed an area of narrowing of the splenic flexure (Fig. 3). Erskine[9] has suggested that congenital intestinal stenoses, such as seen in this patient, may in fact be the result of thromboembolic vascular accidents *in utero* or in the immediate neonatal period. At the time of delivery, a complete knot was noted in the umbilical cord of this patient. Microscopic sections of the portion of the cord between the knot and the placenta revealed evidence of venous congestion, focal hemorrhage, and umbilical vein fibrin thrombi. *Via* the fetal circulatory pathways, these umbilical venous thrombi could have easily embolized to the mesenteric vessels. It has been documented in experimental animals that occlusion or partial occlusion of the mesenteric vasculature of the fetus leads to bowel stenosis or atresia when the animal is delivered a few weeks later.[1,15] It seems reasonable to

postulate that the colonic stenosis in this neonate was the result of such an intrauterine vascular accident.

NONOCCLUSIVE ISCHEMIC BOWEL DISEASE

In neonates it is also possible for intestinal ischemia to develop even when the mesenteric vasculature remains patent. This nonocclusive form of bowel ischemia revolves around the concept of a selective shunting of blood flow away from the splanchnic circulation toward the heart and central nervous system during periods of hypoxia and/or shock. This selective redistribution of blood flow has been linked to the "diving reflex" seen in aquatic mammals.[14] Experimental studies have shown that during these periods of hypoxic stress there is a marked decrease in the perfusion of the stomach, ileum, and colon.[14,23,25]

Necrotizing enterocolitis represents an example of nonocclusive IBD. This is to be differentiated from pneumatosis intestinalis (intramural bowel gas) due to umbilical artery catheters or to mechanical bowel obstruction.[20] The syndrome is characterized by abdominal distention, bilious vomiting and bloody stools; it is most often found in prematures.[20] The early roentgenograms demonstrate multiple distended bowel loops and intramural gas (pneumatosis intestinalis). Complications are portal venous gas and/or bowel perforation. No single mechanism satisfactorily explains all patients with this entity. Most recent investigators agree that infection and hypoxia both play important roles in the pathogenesis of necrotizing enterocolitis.[19,20,22,25]

Regardless of the initiating event, in most cases of necrotizing enterocolitis there is an element of hypoxia which contributes to the pathologic lesion in the intestine. Thus, in the stressed newborn there is a selective shunting of blood away from the splanchnic bed, giving rise to the intestinal ischemia.[14] With progression of the process, the combination of tissue ischemia and bacterial proliferation results in perforation and peritonitis. With less serious ischemia the bowel wall may be able to repair itself, but often with considerable fibrosis and resultant stenosis.

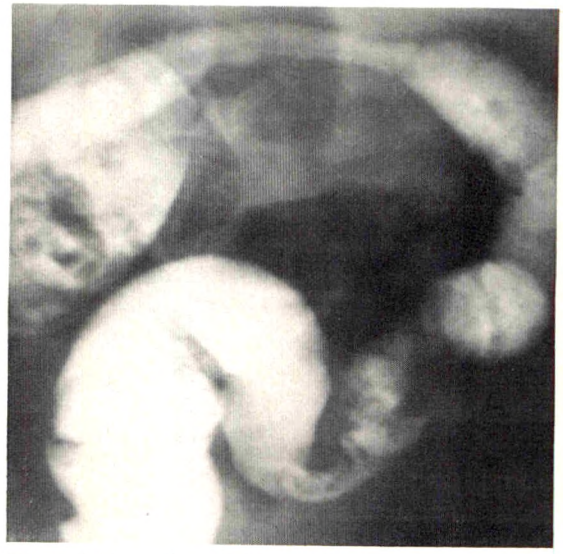

Fig. 4. This patient had necrotizing enterocolitis and was treated medically. Subsequently, he developed this area of stenosis in the transverse colon.

A premature infant that was treated medically for necrotizing enterocolitis survived the acute phase, but 3 weeks later developed a long segment of colonic stenosis (Fig. 4). This complication of an ischemic stricture has also been reported by others.[3,6,11–13,17,21]

As seen in Table 1, there are also other causes of IBD. In the well known neonatal entity of mid gut volvulus, the twisting nature of the volvulus effectively decreases perfusion to the bowel. When this occurs *in utero* or in the perinatal period, the sequela may be stenosis or even atresia of the small bowel.

The incidence of thrombus formation associated with the use of an umbilical arterial catheter is quite high.[26] Mesenteric vascular accidents result from thromboembolic phenomena secondary to these umbilical arterial catheters.[10,20]

Perforation of the nonobstructed bowel occurs following exchange transfusions *via* the umbilical vein.[2,4,16] Clinical information

and experimental data have implicated the umbilical venous catheter as the source of portal hemodynamic or embolic complications which have eventually resulted in an ischemic lesion.[24] Colonic stenosis following repair of this ischemic injury has been reported.

CONCLUSION

With minor degrees of localized ischemia, the bowel may be able to fully recover and return to normal. On the other hand, severe ischemia may result in full thickness necrosis of the bowel wall. Thus, perforation may be an early complication of severe IBD. Between these two opposite ends of the spectrum there will be instances when the degree of ischemia is sufficient to impart considerable damage to the bowel wall, but not enough to cause perforation. Such a damaged bowel can heal by fibrosis with concomitant stricture formation. Thus, ischemic stenosis represents a late complication of IBD.

The radiologist should be aware that a contrast enema examination should not be performed during the acute phase of ischemic enteritis for fear of perforating the already friable bowel wall. Following the acute episode, however, if there are problems with alimentation, a barium enema study and small bowel series should be done to rule out ischemic stricture formation. Likewise, when the radiologist demonstrates an "idiopathic or congenital" stricture in an infant, a careful review of the patient's perinatal history may well uncover a cause for the stenosis (Table 1).

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THE "RECTO-SIGMOID INDEX"*

A MEASUREMENT FOR THE EARLY DIAGNOSIS OF HIRSCHSPRUNG'S DISEASE

By RUBEM POCHACZEVSKY, M.D.,† *and* JOHN C. LEONIDAS, M.D.‡
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THE roentgen diagnosis of Hirschsprung's disease may be established relatively easily when the classic colonic transition segment is identified by contrast enema examination. It may also be suspected if there is prolonged colonic retention of contrast medium. However, a typical transition and/or prolonged colonic stasis may not be apparent during the first days of life.[2,4,5,10,13] Moreover, even in those cases where the presence of transition segments may be subjectively suspected on fluoroscopy, spot film documentation may be incomplete or inconclusive.

Early diagnosis of Hirschsprung's disease, nevertheless, remains a desirable objective, since immediate surgical intervention is of the utmost importance. An objective definition of the colonic transition segment associated with Hirschsprung's disease in the form of a measured range of recto-sigmoid relationships would, therefore, be desirable as an ancillary diagnostic aid. It would be particularly useful in questionable cases, where transition segments are equivocal or not readily demonstrable.

A condition which often mimics Hirschsprung's disease is the meconium plug syndrome.[6,7,10,14–16] Despite several recently outlined roentgen criteria,[10] which were found to be helpful in distinguishing the meconium plug syndrome from Hirschsprung's disease and other pathologic states, it was emphasized[10] that Hirschsprung's disease remained the most difficult

TABLE I

CONTRAST ENEMA EXAMINATIONS IN NEWBORNS WITH HIRSCHSPRUNG'S DISEASE VS. MECONIUM PLUG SYNDROME

Hirschsprung's Disease with No Apparent Transition Segment		Meconium Plug Syndrome	
Patient	"Recto-Sigmoid Index"	Patient	"Recto-Sigmoid Index"
I	0.7	1	1.3
II	0.8	2	1.6
III	0.8	3	1
IV	0.8	4	1.1
V	0.9	5	1.5
VI	0.8	6	1
VII	0.9	7	1.7
VIII	0.7	8	1
IX	0.7	9	1.8
X	0.7	10	1.4
Mean Value	0.8		1.3

* From the Departments of Radiology of Mount Sinai Hospital Services, the City Hospital Center at Elmhurst, Mount Sinai School of Medicine, City University of New York, New York,† and the Children's Mercy Hospital, the University of Missouri School of Medicine, Kansas City, Missouri.‡

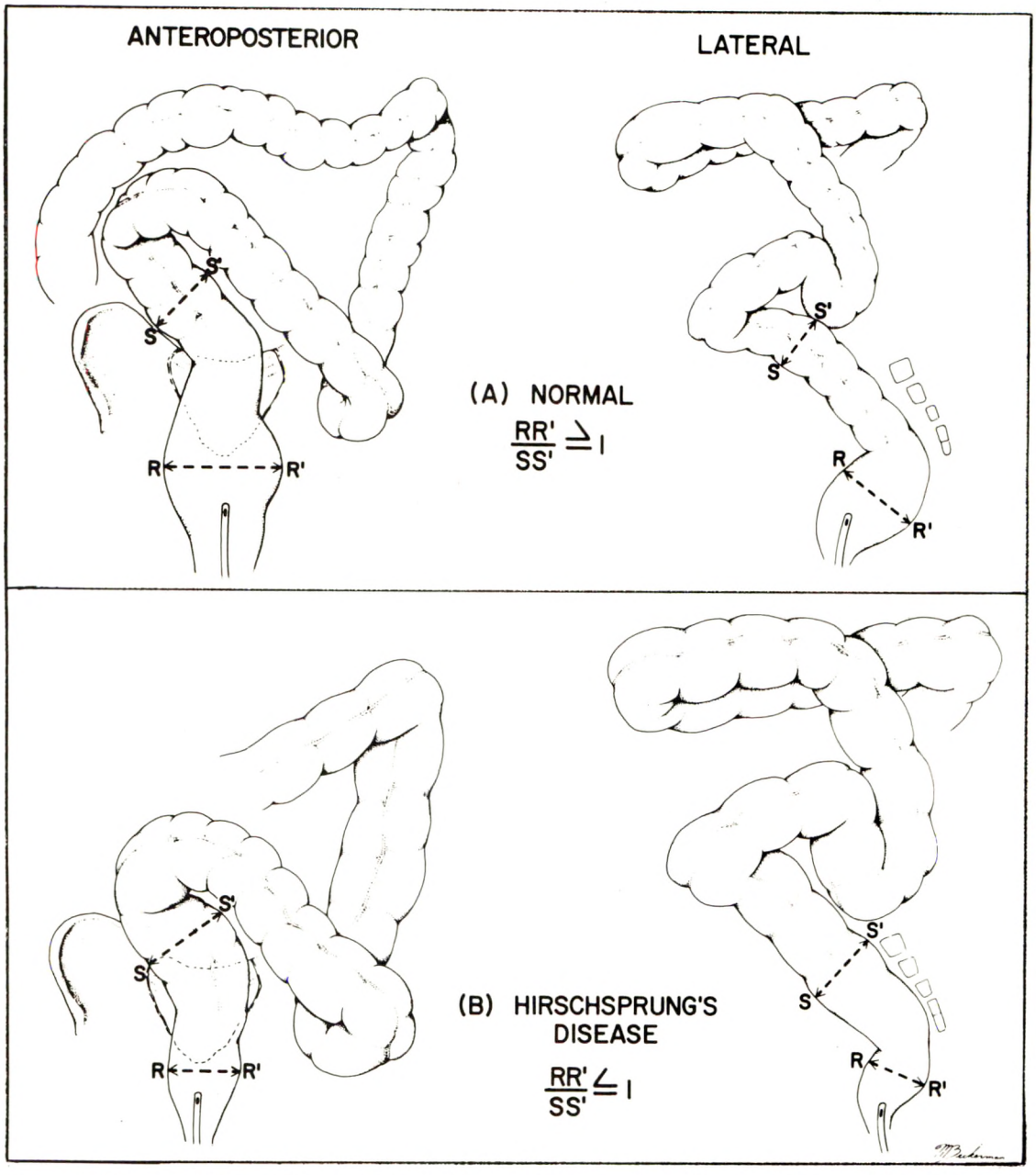

Fig. 1. (*A*) Normal "Recto-Sigmoid Index:" The ratio between the widest diameter of the rectum (RR′) and the widest diameter of the sigmoid (SS′) is larger or equal to 1; (*B*) abnormal "Recto-Sigmoid Index:" Hirschsprung's disease. The ratio is smaller than 1.

problem in differential diagnosis in view of occasional, but almost identical, clinical and roentgen findings.

The "Recto-Sigmoid Index"

In an attempt to strengthen current roentgen diagnostic criteria as they apply to Hirschsprung's disease, our material of Hirschsprung's disease was reviewed. It has been our experience that the widest rectal diameter is usually smaller than the widest diameter of the sigmoid loop in Hirschsprung's disease, even in the absence of a roentgenographically definite transi-

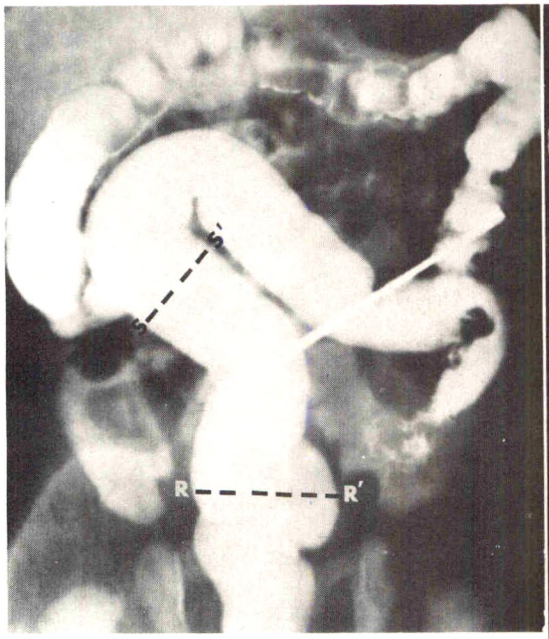

Fig. 2. Normal barium enema in a 2 day old female with a history of a mild episode of rectal bleeding. Long term follow-up did not disclose any clinical evidence of Hirschsprung's disease. Note that the rectum is wider than the sigmoid loop. The "Recto-Sigmoid Index" (RR′/SS′) is 1.4.

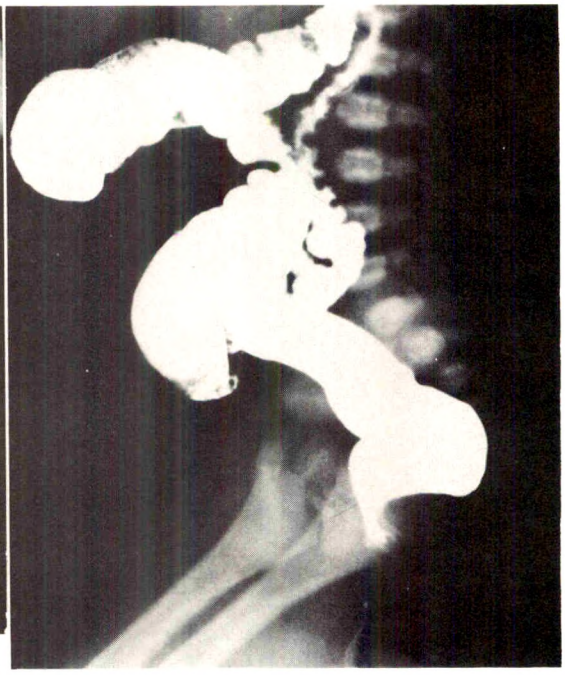

Fig. 3. Normal barium enema in a newborn female. The contrast study was performed to determine cause of a single occurrence of rectal bleeding. The infant remained well for over 2 years with no clinical evidence of Hirschsprung's disease. The "Recto-Sigmoid Index" in this lateral view is 1.3.

tion segment. In normal newborn infants, as well as in cases of the meconium plug syndrome and other pathologic states, the rectum was commonly found to be wider than the sigmoid loop. A numerical index was obtained in our review by dividing the widest diameter of the rectum by the widest diameter of the sigmoid loop, the "Recto-Sigmoid Index."

Table II

NORMAL CONTRAST ENEMA EXAMINATIONS IN 12 NEWBORNS

Patient	History	"Recto-Sigmoid Index"
I	Mild diarrhea	1.9
II	Poor feeding, vomiting	1.5
III	Rectal bleeding	1.4
IV	Poor feeding, vomiting	1.5
V	Rectal bleeding	1.0
VI	Rectal bleeding	1.4
VII	Vomiting	1.1
VIII	Vomiting	1.5
IX	Vomiting	1.4
X	Vomiting and diarrhea	1.7
XI	Abdominal distention	1.0
XII	Abdominal distention	1.2
Mean Value		1.4

Table III

CONTRAST ENEMA EXAMINATIONS IN NEWBORNS WITH MISCELLANEOUS PATHOLOGY OF THE GASTROINTESTINAL TRACT

Patient	Diagnosis	"Recto-Sigmoid Index"
I	Meconium ileus	1.5
II	Midgut malrotation	1.4
III	Gastroschisis, post-operative	1.3
IV	Necrotizing enterocolitis of infancy	1.3
V	Jejunal atresia	1.3
Mean Value		1.4

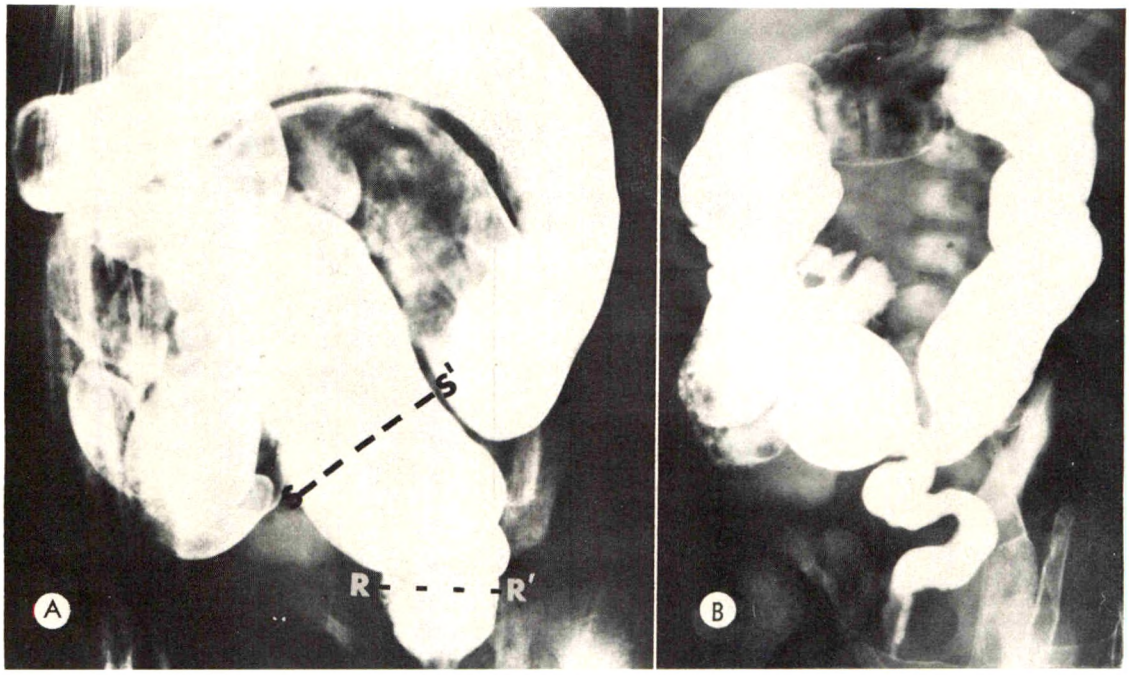

Fig. 4. Case 1. Newborn female with history of abdominal distention.
(*A*) Barium enema examination performed at 3 days of age. A transition segment is not apparent. The rectum, however, is narrower than the sigmoid. The "Recto-Sigmoid Index" (RR'/SS') measures 0.8 in this projection. (*B*) Repeat barium enema examination performed 1 week later. An obvious transition segment involving the rectum and distal segment is now present.

MATERIAL AND METHOD

The case material studied consisted of 21 biopsy proven cases of Hirschsprung's disease, 10 cases of the meconium plug syndrome and 12 cases of term newborn infants considered to be normal. Five cases of the authors' material of other diseases of the gastrointestinal tract including necrotizing enterocolitis of infancy,[9] meconium ileus[8] and midgut volvulus were also reviewed. All cases were studied with contrast enemas within the first 7 days of life, with the majority being examined during the first 4 days. All infants with the meconium plug syndrome, other gastrointestinal disease, and "normal" babies have been followed clinically for a period of at least 2 years and demonstrated no clinical evidence of Hirschsprung's disease.

Regarding the "normal" controls, these were infants who had a variety of mild disorders from poor feeding, vomiting and mild diarrhea, to unexplained mild rectal bleeding for which no cause was revealed. In all instances, the contrast enemas were normal and there has been no evidence of gastrointestinal disorder. No rectal biopsies have been performed, however, in any of the control patients. We believe that it can be safely assumed that they do not have Hirschsprung's disease.

In each instance, the widest diameter of the rectum was obtained at any level below the 3rd sacral vertebra. This point was established arbitrarily on the basis of the usual position of transition segments. The sigmoid loop was usually measured at 3 points along its course (proximal, peak of the loop and distal sigmoid colon). The largest measurement was selected. In almost all instances the widest part of the sigmoid proved to be the distal sigmoid loop. All measurements were obtained along a transverse axis, vertical to the longitudinal axis of the colon at that point (Fig. 1, *A* and *B*).

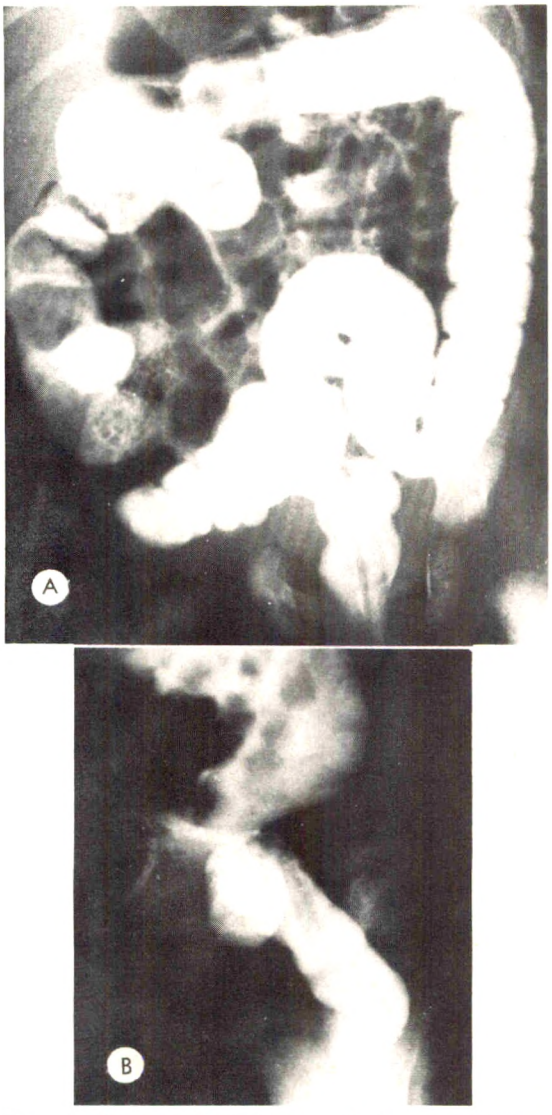

Fig. 5. Case II. Hirschsprung's disease. Barium enema examination performed at 2 days of age.

(*A*) Anteroposterior projection. (*B*) Lateral view. A definite transition segment could not be identified in this study, although the rectum appears to be of slightly smaller caliber than the sigmoid. The average "Recto-Sigmoid Index" in this study is 0.9. A repeat barium enema study performed 2 months later showed a definite transition segment.

Measurements were made in 3 projections, including anteroposterior, left posterior oblique and lateral. The "Recto-Sigmoid Index" was obtained by dividing the widest diameter of the rectum by the widest diameter of the sigmoid loop when the colon was fully distended by contrast medium. Although absolute numbers varied according to the projection, the index proved to be fairly constant in any of the above projections, so that they consistently averaged out (Fig. 1, *A* and *B*).

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RESULTS

Among the 21 cases of Hirschsprung's disease, no definite or only a questionable colonic transition segment could be identified in 10 cases on the first contrast study. The average values of the "Recto-Sigmoid Index" taken in multiple projections of the latter 10 cases ranged from 0.7 to 0.9 with a mean value of 0.8 (Fig. 4–7; and Table I).

The average "Recto-Sigmoid Index" in the 12 normal newborns ranged from 1 to 1.9 with a mean value of 1.4 (Table II; and Fig. 2; and 3).

The "Recto-Sigmoid Index" was above

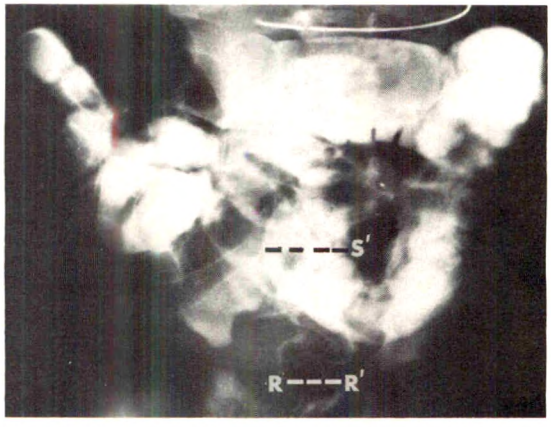

Fig. 6. Case III. Hirschsprung's disease. Contrast enema examination performed at 1 day of age. Anteroposterior projection. The rectum is not as wide as the sigmoid. The "Recto-Sigmoid Index" (RR'/SS') in this projection measures 0.6.

1 in all 5 cases of newborns with other pathologic processes of the gastrointestinal tract, with values ranging from 1.3 to 1.5 and the mean of 1.4 (Table III; and Fig. 9; and 10). A limited selective review of the literature[2–10,13–15] was also undertaken and the "Recto-Sigmoid Index" was calculated when feasible. The results appeared to confirm the measurements of our own cases.

DISCUSSION

The above results suggest that the "Recto-Sigmoid Index" may be of value in the diagnosis of Hirschsprung's disease in the first few days of life, in the absence of a definite roentgenographic transition segment on contrast enemas (Fig. 4*A*; and 5–7). A "Recto-Sigmoid Index" of less than

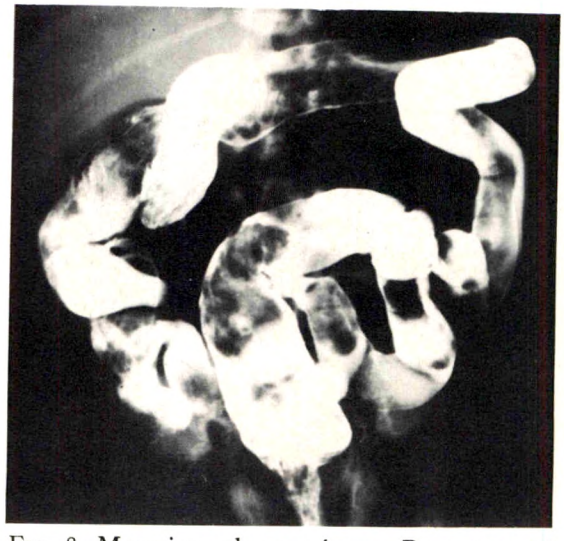

Fig. 8. Meconium plug syndrome. Premature, 18 hour old male with a history of abdominal distention and failure to pass meconium. The barium enema examination shows large intracolonic meconium masses. The rectum is wider than the sigmoid. The "Recto-Sigmoid Index" in this projection is 1.3. A large meconium plug was passed following completion of the study.

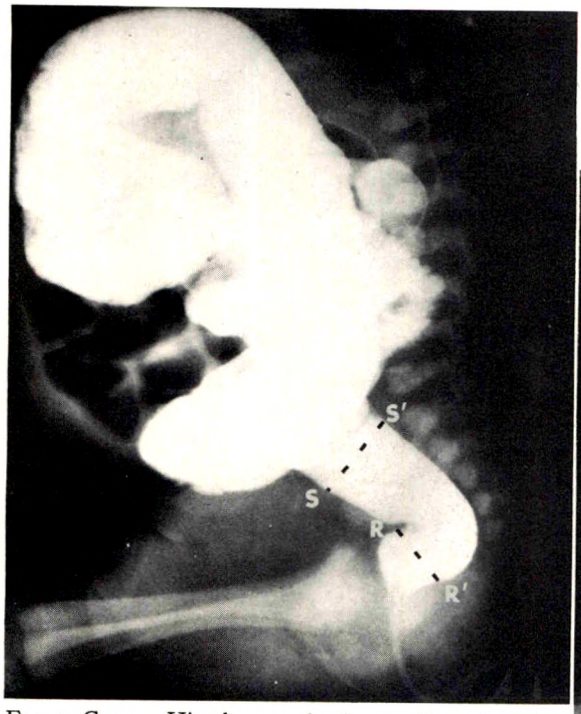

Fig. 7. Case x. Hirschsprung's disease. Four day old male with history of failure to pass meconium and abdominal distention. Contrast enema examination revealed only a questionable transitional segment. The "Recto-Sigmoid Index" (RR'/SS') measures 0.7 in this lateral view. (Courtesy of Dr. Henry Pritzker, Montefiore Hospital and Medical Center, New York City.)

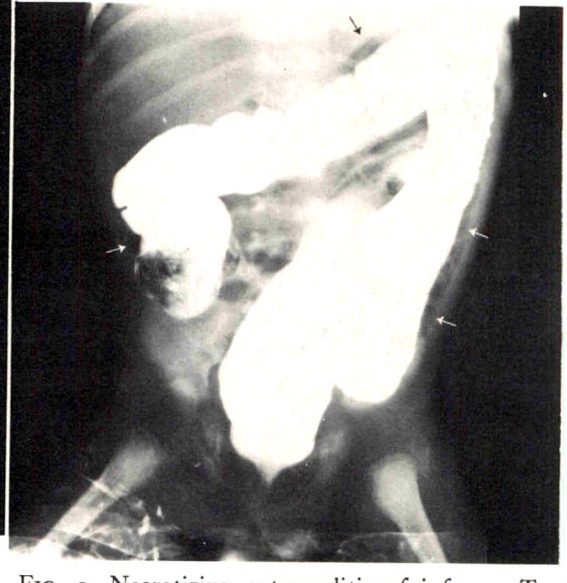

Fig. 9. Necrotizing enterocolitis of infancy. Two week old male. The barium enema examination demonstrates extensive pneumatosis intestinalis (arrows). The rectum is, however, wider than the sigmoid loop. The "Recto-Sigmoid Index" measures 1.3. Measurements were also based on oblique and lateral views.

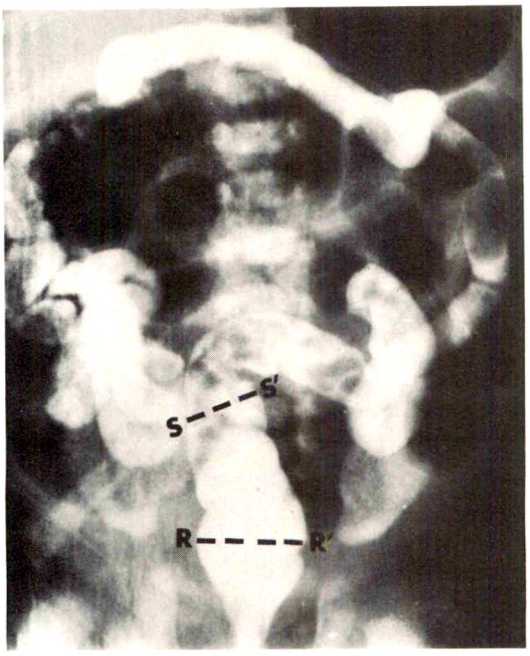

Fig. 10. Lower jejunal atresia. Newborn infant. The contrast enema examination demonstrates a microcolon. Nevertheless, the caliber of the rectum is larger than the sigmoid loop. The "Recto-Sigmoid Index" (RR'/SS') measures 1.3.

1 would be suggestive of Hirschsprung's disease.

The "Recto-Sigmoid Index" is obviously superfluous when a transition segment is clearly evident in the form of marked disproportion between the rectum and the proximal sigmoid colon (Fig. 4*B*). A less definite disproportion in the caliber of the distal aganglionic and normal proximal colon may be appreciated by the most experienced observers. However, we have seen considerable confusion and missed diagnoses in subtle cases. It is hoped that determination of the "Recto-Sigmoid Index" will provide a further diagnostic aid when a zone of transition is in doubt. The "Recto-Sigmoid Index" was not intended to be used in the rarer instances of aganglionosis involving other loci of the colon or with more extensive aganglionosis, including total aganglionosis of the colon and terminal ileum.[1,2] The recto-sigmoid area remains, however, the most common site for the aganglionic segments of Hirschsprung's disease.[5] All of our cases of Hirschsprung's disease were confined to this location and the measurements may, therefore, serve as an aid to diagnosis in this region.

In the meconium plug syndrome (Fig. 8; and Table 1) and in other pathologic conditions which may simulate Hirschsprung's disease[10] (Fig. 9; and 10) as well as in normal newborn infants (Fig. 2; and 3), the "Recto-Sigmoid Index" was almost invariably higher or at least equal to 1. A "Recto-Sigmoid Index" higher than 1 tended to exclude the diagnosis of Hirschsprung's disease in the current material. It should be noted, however, that in view of the limited number of cases collected and the known difficulty of establishing the diagnosis of colonic aganglionosis in early life, a rectal biopsy may be necessary in clinically borderline cases despite a "Recto-Sigmoid Index" higher than 1.

SUMMARY

The "Recto-Sigmoid Index" is an objective measurement which may prove to be useful in the early diagnosis of Hirschsprung's disease in the newborn, particularly in those cases where a colonic transition segment is not readily apparent or where its presence is questionable.

On the basis of our current case material, a "Recto-Sigmoid Index" higher than 1 may indicate a normal colon or a condition mimicking Hirschsprung's disease, such as meconium plug syndrome.

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PRUNE BELLY SYNDROME*

AN UNUSUAL CAUSE OF NEONATAL ABDOMINAL CALCIFICATION

By DONALD R. KIRKS, M.D.,† *and* HOOSHANG TAYBI, M.D.‡
OAKLAND, CALIFORNIA

THE prune belly syndrome is a well-known entity with characteristic clinical, radiologic, and pathologic features.[7,9,12,20,24,27] Mareschal and associates[15] have referred to perivesical calcification in 2 patients with this syndrome. However, abdominal calcification was not mentioned in a recent review of 245 reported cases of this entity.[30]

The radiologic findings and pathologic correlation of abdominal calcification in 2 patients with the prune belly syndrome are presented.

REPORT OF CASES

CASE 1. D.M. was a 2.5 kg. male delivered to an 18 year old Gravida 1, Para 0 white female. Pregnancy and delivery were both normal. Physical examination revealed wrinkled abdominal skin, bulging flanks, left club foot, absence of the right foot and ankle, undescended testicles, and bilateral cystic flank masses.

A chest roentgenogram showed a left pneumothorax and pneumomediastinum. An abdominal roentgenogram at 3 days of age demonstrated classic radiologic features of the prune belly syndrome. In addition, amorphous calci-

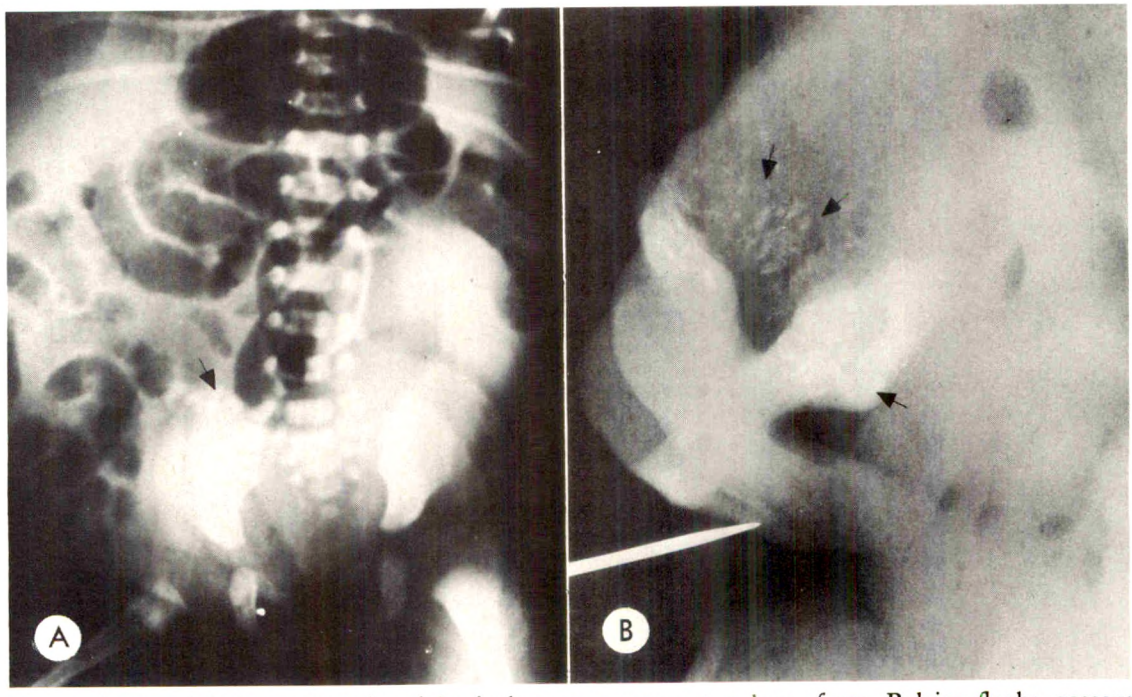

FIG. 1. Case 1. (*A*) Anteroposterior abdominal roentgenogram at 3 days of age. Bulging flanks, gaseous distention, flared lower ribs, and flared iliac wings are noted. In addition, an irregular calcific density (arrow) is seen in the lower abdomen. (*B*) Roentgenogram of pathologic specimen. Numerous calcific densities (arrows) are present in the wall of the urachal cyst.

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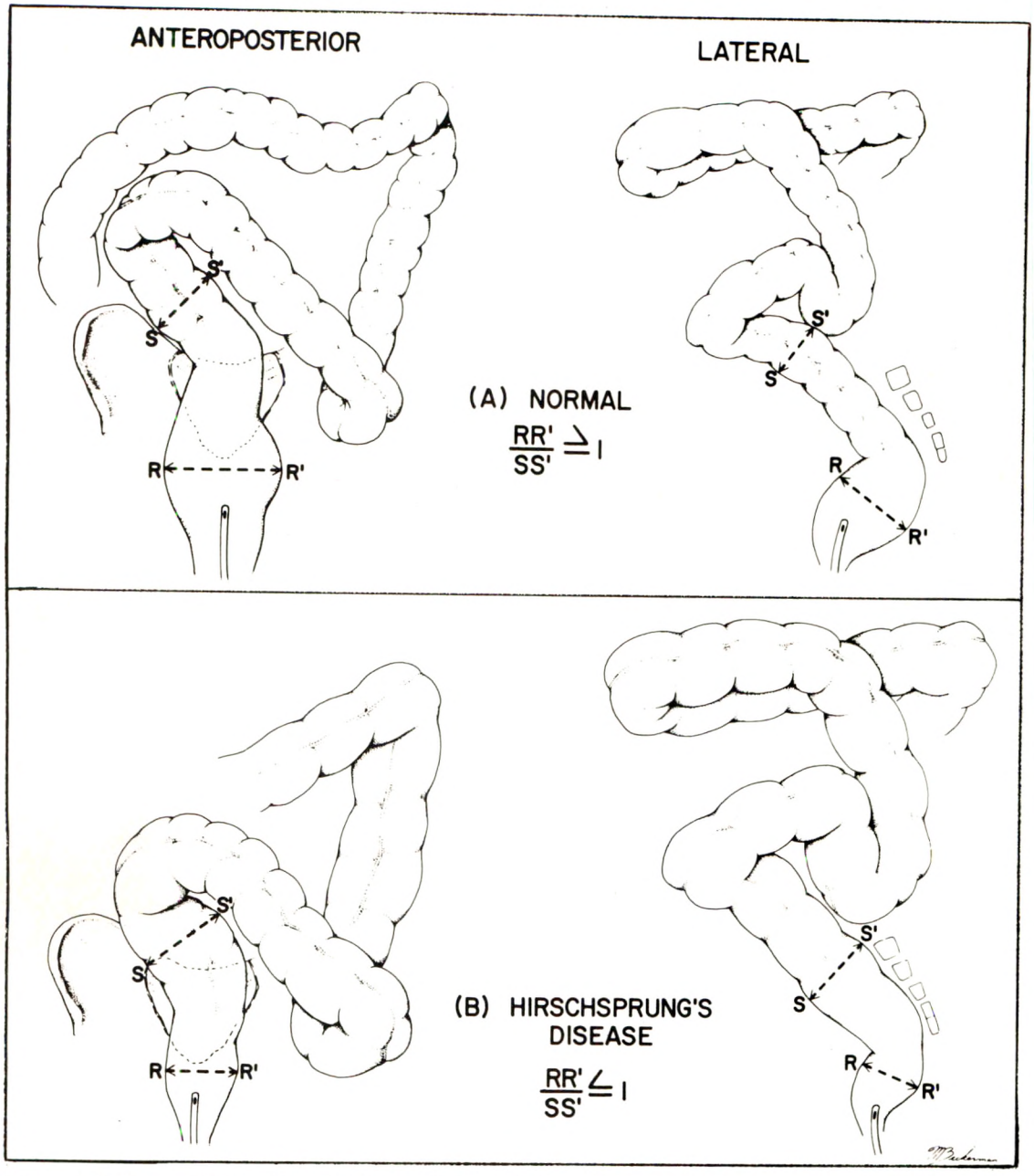

Fig. 1. (*A*) Normal "Recto-Sigmoid Index:" The ratio between the widest diameter of the rectum (RR′) and the widest diameter of the sigmoid (SS′) is larger or equal to 1; (*B*) abnormal "Recto-Sigmoid Index:" Hirschsprung's disease. The ratio is smaller than 1.

problem in differential diagnosis in view of occasional, but almost identical, clinical and roentgen findings.

The "Recto-Sigmoid Index"

In an attempt to strengthen current roentgen diagnostic criteria as they apply to Hirschsprung's disease, our material of Hirschsprung's disease was reviewed. It has been our experience that the widest rectal diameter is usually smaller than the widest diameter of the sigmoid loop in Hirschsprung's disease, even in the absence of a roentgenographically definite transi-

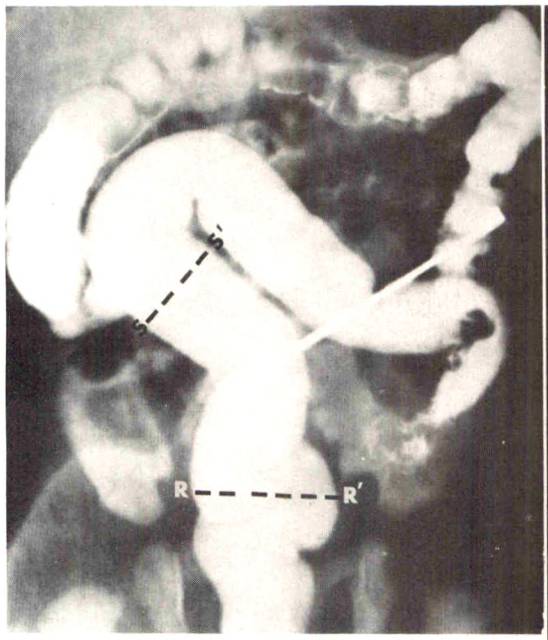

FIG. 2. Normal barium enema in a 2 day old female with a history of a mild episode of rectal bleeding. Long term follow-up did not disclose any clinical evidence of Hirschsprung's disease. Note that the rectum is wider than the sigmoid loop. The "Recto-Sigmoid Index" (RR'/SS') is 1.4.

FIG. 3. Normal barium enema in a newborn female. The contrast study was performed to determine cause of a single occurrence of rectal bleeding. The infant remained well for over 2 years with no clinical evidence of Hirschsprung's disease. The "Recto-Sigmoid Index" in this lateral view is 1.3.

tion segment. In normal newborn infants, as well as in cases of the meconium plug syndrome and other pathologic states, the rectum was commonly found to be wider than the sigmoid loop. A numerical index was obtained in our review by dividing the widest diameter of the rectum by the widest diameter of the sigmoid loop, the "Recto-Sigmoid Index."

TABLE II

NORMAL CONTRAST ENEMA EXAMINATIONS IN 12 NEWBORNS

Patient	History	"Recto-Sigmoid Index"
I	Mild diarrhea	1.9
II	Poor feeding, vomiting	1.5
III	Rectal bleeding	1.4
IV	Poor feeding, vomiting	1.5
V	Rectal bleeding	1.0
VI	Rectal bleeding	1.4
VII	Vomiting	1.1
VIII	Vomiting	1.5
IX	Vomiting	1.4
X	Vomiting and diarrhea	1.7
XI	Abdominal distention	1.0
XII	Abdominal distention	1.2
Mean Value		1.4

TABLE III

CONTRAST ENEMA EXAMINATIONS IN NEWBORNS WITH MISCELLANEOUS PATHOLOGY OF THE GASTROINTESTINAL TRACT

Patient	Diagnosis	"Recto-Sigmoid Index"
I	Meconium ileus	1.5
II	Midgut malrotation	1.4
III	Gastroschisis, post-operative	1.3
IV	Necrotizing enterocolitis of infancy	1.3
V	Jejunal atresia	1.3
Mean Value		1.4

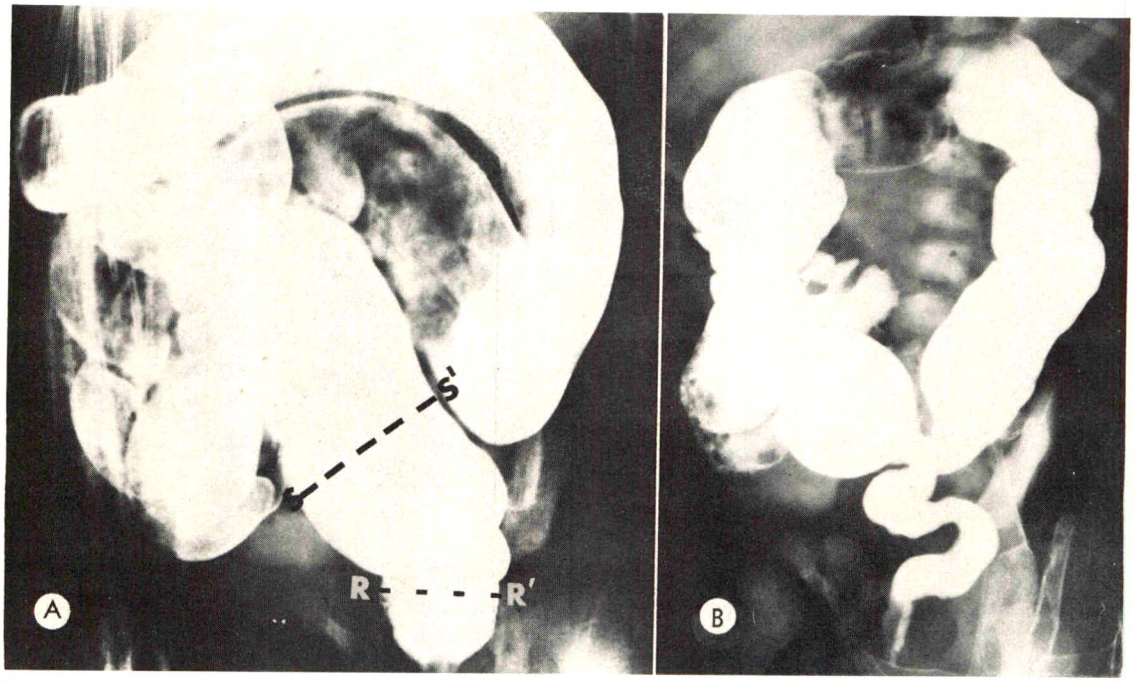

Fig. 4. Case 1. Newborn female with history of abdominal distention.
(*A*) Barium enema examination performed at 3 days of age. A transition segment is not apparent. The rectum, however, is narrower than the sigmoid. The "Recto-Sigmoid Index" (RR'/SS') measures 0.8 in this projection. (*B*) Repeat barium enema examination performed 1 week later. An obvious transition segment involving the rectum and distal segment is now present.

MATERIAL AND METHOD

The case material studied consisted of 21 biopsy proven cases of Hirschsprung's disease, 10 cases of the meconium plug syndrome and 12 cases of term newborn infants considered to be normal. Five cases of the authors' material of other diseases of the gastrointestinal tract including necrotizing enterocolitis of infancy,[9] meconium ileus[8] and midgut volvulus were also reviewed. All cases were studied with contrast enemas within the first 7 days of life, with the majority being examined during the first 4 days. All infants with the meconium plug syndrome, other gastrointestinal disease, and "normal" babies have been followed clinically for a period of at least 2 years and demonstrated no clinical evidence of Hirschsprung's disease.

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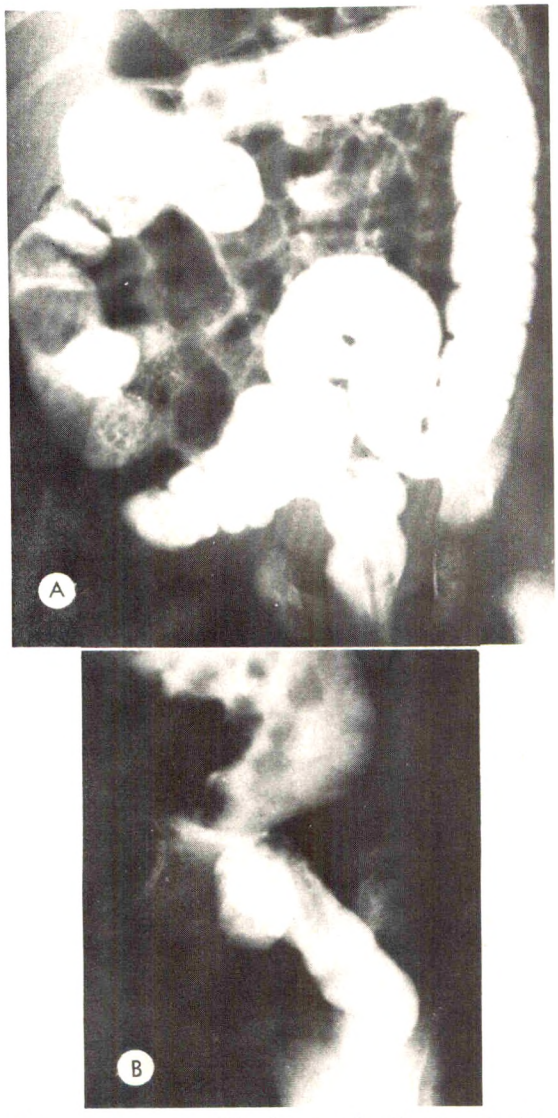

Fig. 5. Case 11. Hirschsprung's disease. Barium enema examination performed at 2 days of age.

(*A*) Anteroposterior projection. (*B*) Lateral view. A definite transition segment could not be identified in this study, although the rectum appears to be of slightly smaller caliber than the sigmoid. The average "Recto-Sigmoid Index" in this study is 0.9. A repeat barium enema study performed 2 months later showed a definite transition segment.

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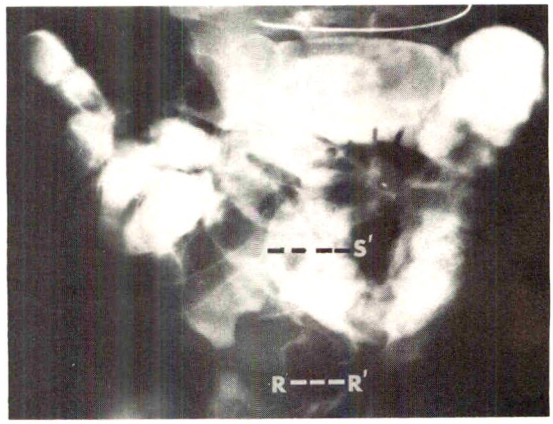

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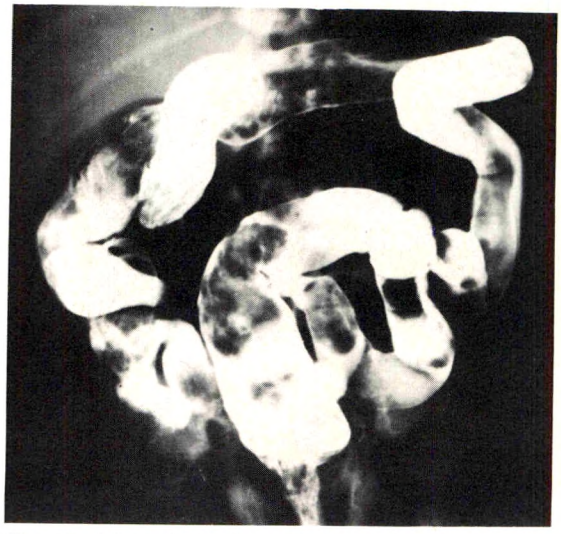
The above results suggest that the "Recto-Sigmoid Index" may be of value in the diagnosis of Hirschsprung's disease in the first few days of life, in the absence of a definite roentgenographic transition segment on contrast enemas (Fig. 4*A*; and 5–7). A "Recto-Sigmoid Index" of less than



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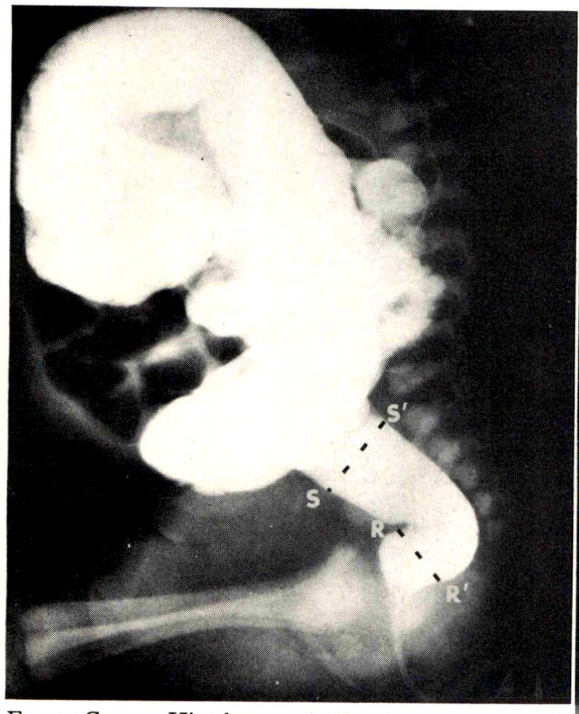

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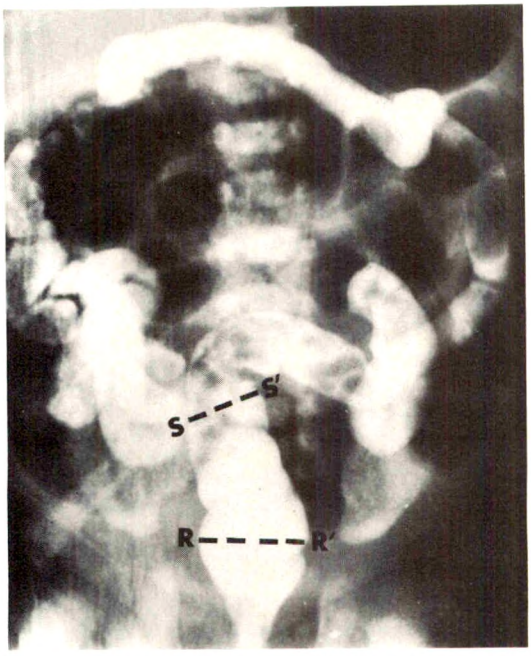

Fig. 10. Lower jejunal atresia. Newborn infant. The contrast enema examination demonstrates a microcolon. Nevertheless, the caliber of the rectum is larger than the sigmoid loop. The "Recto-Sigmoid Index" (RR'/SS') measures 1.3.

1 would be suggestive of Hirschsprung's disease.

The "Recto-Sigmoid Index" is obviously superfluous when a transition segment is clearly evident in the form of marked disproportion between the rectum and the proximal sigmoid colon (Fig. 4*B*). A less definite disproportion in the caliber of the distal aganglionic and normal proximal colon may be appreciated by the most experienced observers. However, we have seen considerable confusion and missed diagnoses in subtle cases. It is hoped that determination of the "Recto-Sigmoid Index" will provide a further diagnostic aid when a zone of transition is in doubt. The "Recto-Sigmoid Index" was not intended to be used in the rarer instances of aganglionosis involving other loci of the colon or with more extensive aganglionosis, including total aganglionosis of the colon and terminal ileum.[1,2] The recto-sigmoid area remains, however, the most common site for the aganglionic segments of Hirschsprung's disease.[5] All of our cases of Hirschsprung's disease were confined to this location and the measurements may, therefore, serve as an aid to diagnosis in this region.

In the meconium plug syndrome (Fig. 8; and Table 1) and in other pathologic conditions which may simulate Hirschsprung's disease[10] (Fig. 9; and 10) as well as in normal newborn infants (Fig. 2; and 3), the "Recto-Sigmoid Index" was almost invariably higher or at least equal to 1. A "Recto-Sigmoid Index" higher than 1 tended to exclude the diagnosis of Hirschsprung's disease in the current material. It should be noted, however, that in view of the limited number of cases collected and the known difficulty of establishing the diagnosis of colonic aganglionosis in early life, a rectal biopsy may be necessary in clinically borderline cases despite a "Recto-Sigmoid Index" higher than 1.

SUMMARY

The "Recto-Sigmoid Index" is an objective measurement which may prove to be useful in the early diagnosis of Hirschsprung's disease in the newborn, particularly in those cases where a colonic transition segment is not readily apparent or where its presence is questionable.

On the basis of our current case material, a "Recto-Sigmoid Index" higher than 1 may indicate a normal colon or a condition mimicking Hirschsprung's disease, such as meconium plug syndrome.

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PRUNE BELLY SYNDROME*

AN UNUSUAL CAUSE OF NEONATAL ABDOMINAL CALCIFICATION

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THE prune belly syndrome is a well-known entity with characteristic clinical, radiologic, and pathologic features.[7,9,12,20,24,27] Mareschal and associates[15] have referred to perivesical calcification in 2 patients with this syndrome. However, abdominal calcification was not mentioned in a recent review of 245 reported cases of this entity.[30]

The radiologic findings and pathologic correlation of abdominal calcification in 2 patients with the prune belly syndrome are presented.

REPORT OF CASES

CASE 1. D.M. was a 2.5 kg. male delivered to an 18 year old Gravida 1, Para 0 white female. Pregnancy and delivery were both normal. Physical examination revealed wrinkled abdominal skin, bulging flanks, left club foot, absence of the right foot and ankle, undescended testicles, and bilateral cystic flank masses.

A chest roentgenogram showed a left pneumothorax and pneumomediastinum. An abdominal roentgenogram at 3 days of age demonstrated classic radiologic features of the prune belly syndrome. In addition, amorphous calci-

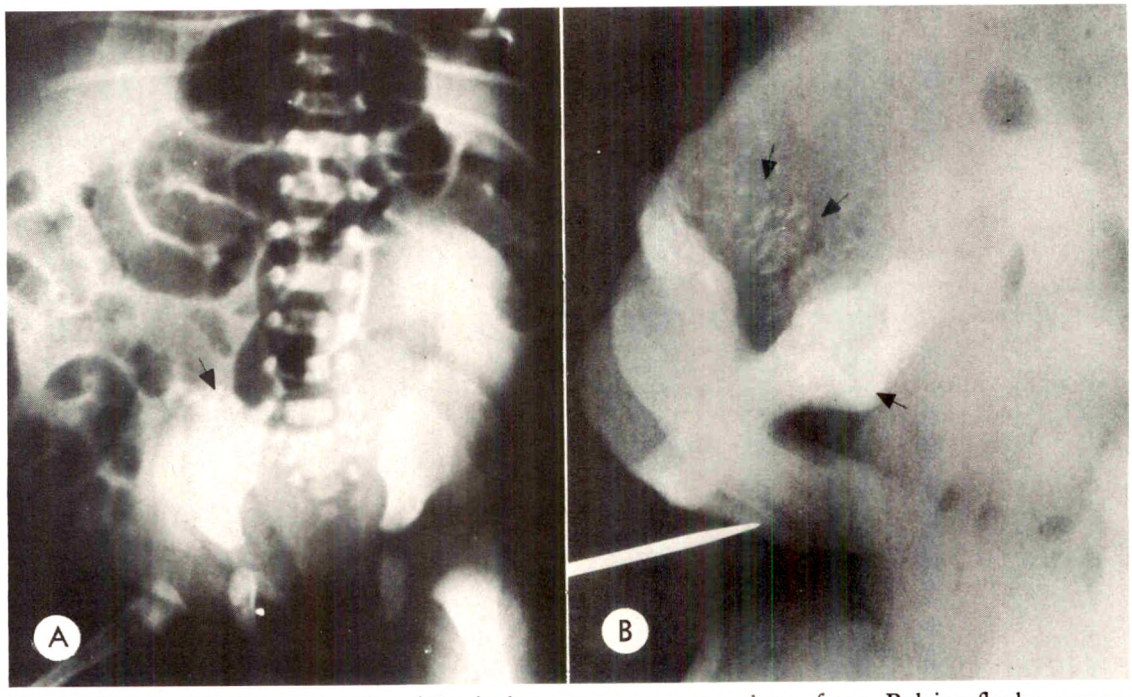

FIG. 1. Case 1. (*A*) Anteroposterior abdominal roentgenogram at 3 days of age. Bulging flanks, gaseous distention, flared lower ribs, and flared iliac wings are noted. In addition, an irregular calcific density (arrow) is seen in the lower abdomen. (*B*) Roentgenogram of pathologic specimen. Numerous calcific densities (arrows) are present in the wall of the urachal cyst.

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fications were noted in the right lower abdomen (Fig. 1*A*). Voiding cystourethrography demonstrated a large trabeculated bladder, patent urachus, gross vesico-ureteral reflux, hydronephrosis, bulging of the bladder base, a dilated utricle, and a small urethra.

Due to poor intake, gavage feedings were begun at 2 days of age. On the fifth day of life, sudden hypothermia was followed by cardiac arrest. Postmortem blood cultures grew *Escherichia coli*.

At autopsy, the mesentery of bowel was redundant and both testicles were intra-abdominal. There was hemimelia of the right lower extremity. Both kidneys were in the left upper quadrant. The bladder was enlarged and both ureters were massively dilated. A urachal cyst communicated with the dome of the bladder and extended to the umbilicus.

Histologic examination of the kidneys showed marked disorganization of normal parenchyma with fibrous connective tissue proliferation. The bladder wall was almost completely replaced by fibrous tissue. Varying sized foci of calcification, measuring up to 8 mm. in diameter, were present in the wall of the urachal cyst (Fig. 1*B*).

Case II. K.T. was a 2.5 kg. male delivered to an 18 year old Gravida 1, Para 0 Black female. Pregnancy, labor, and delivery were uncomplicated. Wrinkled abdominal skin, undescended testes, bilateral club feet, bilateral flank masses, and a 6 cm. in diameter pelvic mass were present at birth.

An initial roentgenogram of the abdomen at 3 days of age demonstrated findings of the prune belly syndrome. A 15 mm. in diameter collection of calcific densities was noted lying in relationship to the dome of the distended bladder (Fig. 2*A*). Excretory urography did not visualize the upper urinary tracts. An enlarged bladder, patent urachus, vesico-ureteral reflux, dilated ureters, and tapering of the bladder base were demonstrated by cystography.

At 4 months of age, the patient was readmitted with fever and anorexia. Despite antibiotic therapy, the patient had a cardiac arrest and expired.

At autopsy, both testicles were in the abdomen. There was absence of the mesocolon but no evidence of malrotation. The bladder and both ureters were enlarged.

Both kidneys were dysplastic with primitive

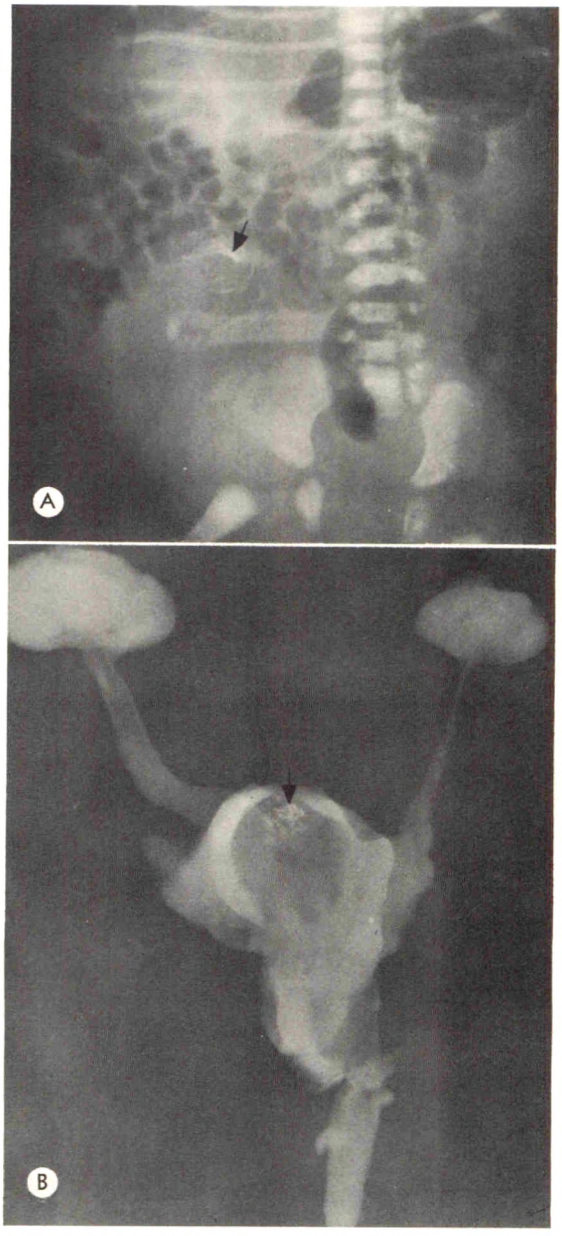

Fig. 2. Case II. (*A*) Anteroposterior abdominal roentgenogram at 3 days of age. Flared lower ribs, bulging flanks, and flared iliac wings are seen. The pubic bones are not ossified. A circular calcific density (arrow) is present, lying in relationship to the top of a soft tissue mass density. (*B*) Roentgenogram of pathologic specimen. Circular collection of calcific densities (arrow) is present in the dome of the bladder. Note the shrunken appearance of the dysplastic kidneys.

TABLE I

CAUSES OF NEONATAL ABDOMINAL CALCIFICATION

- Abdominal Wall
  - Fat necrosis[8]
  - Calcium salt injection[3]
  - Generalized fibromatosis[11]
  - Osteomas of skin[29]
- Peritoneal
  - Meconium peritonitis
  - Plastic peritonitis due to hydrometrocolpos[6]
- Hepatic
  - Primary tumor
    - Hemangioma[2]
    - Hemangioendothelioma[17]
    - Hepatoblastoma[7a]
  - Metastatic tumor
    - Neuroblastoma
  - Portal vein thromboemboli[4]
  - Post umbilical vein catheterization[1]
- Gastrointestinal
  - Meconium in bowel or cloaca[10]
  - Infarcted bowel
  - Intramural in bowel obstruction[28]
- Retroperitoneal
  - Adrenal
    - Adrenal hemorrhage
    - Neuroblastoma
    - Wolman's disease
    - Carcinoma[26]
  - Renal
    - Cortical necrosis[13]
    - Papillary necrosis[18]
    - Renal vein thrombosis[17a]
  - Teratoma[22]
- Scrotal
  - Meconium peritonitis
  - Teratoma[22]
- Vascular
  - Idiopathic arterial calcification[14]
  - Portal vein thromboemboli[4]
  - Inferior vena cava thrombus[25]
  - Renal vein thrombosis[17a]
- Miscellaneous
  - Teratoma, fetus in fetu[22,19]
  - Ovarian dermoid
  - Prune belly syndrome

tubules, fibrous tissue, and epithelial-lined cortical cysts. Calcific densities were present in the dome of the bladder (Fig. 2*B*). Histologically, this calcification was located in the inner one-half of the bladder wall and was surrounded by mononuclear cells and fibroblasts. These changes were felt to be consistent with necrosis and subsequent dystrophic calcification.

DISCUSSION

The classic triad of the prune belly syndrome is hypoplasia of abdominal muscles, undescended testicles, and abnormalities of the urinary system. Other associated clinical abnormalities such as microcephaly, scoliosis, hip dislocation, foot and leg deformities, polydactyly, syndactyly, pectus deformities, congenital heart disease, intestinal malrotation, and imperforate anus have been reported.[20,23,27,30,31] Pathologically, the kidneys show a decrease in the number of functioning nephrons as well as various degrees of dysplasia with cystic change. The ureters and bladder show patchy absence of smooth muscle with replacement by fibrous collagenous tissue.[5,21,23]

A variety of radiologic findings in this syndrome have been described.[7,9,12,24,30] These abnormalities may include bulging flanks, gaseous distention of bowel, flaring of lower ribs, flared iliac wings, decreased iliac indices, wide interpubic distance, renal agenesis, hydronephrosis, ureteral atresia, trabeculated bladder tapering toward umbilical attachment, bladder diverticula, patent urachus, vesicoureteral reflux, tapering of bladder base extending to posterior urethra, dilated prostatic utricle, urethral valve, urethral diverticulum, urethral stenosis, urethral atresia, and megalourethra.

Because of these 2 interesting patients, all other cases of the prune belly syndrome at this hospital between 1968 and 1974 were reviewed. Abdominal roentgenograms of 6 other patients with this syndrome were available for review. In no other instance was abdominal calcification identified.

The etiology of calcification within the abnormal urinary system of these 2 patients is unknown. The histology suggests that these are dystrophic calcifications which develop in a congenitally abnormal urinary tract.

There are numerous causes of abdominal calcification in the neonate[16,26] (Table 1). Calcification in the abnormal urinary tract of the patient with the prune belly syn-

drome should be added to this differential diagnosis.

SUMMARY

Two cases of abdominal calcification in newborns with the prune belly syndrome are reported. These calcifications were in a urachal cyst and in the dome of the bladder.

A differential diagnosis of neonatal abdominal calcification is presented.

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FAMILIAL COLON CARCINOMA IN NAIL-PATELLA SYNDROME*

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NAIL-PATELLA syndrome, onycho-osteodysplasia, has been well described in past literature.[4,6,10,13,21,22,25] Nail and patellar hypoplasia, iliac horns,[9] and elbow dysplasia are the main roentgenographic findings in this syndrome. A patient and her family exhibiting these features have a history compatible with familial colon carcinoma. This association has not been previously reported.

Nail-patella syndrome has been linked to the ABO blood groups and adenylate kinase, and since colon carcinoma segregates with nail-patella syndrome in 3 family members, it may belong to this linkage group. Two newly recognized skeletal findings will be presented. In a subsequent paper, measurement guidelines for hypoplastic patellae will be described.

CASE MATERIAL

A 47 year old intelligent white female was followed for recurrent sinusitis and arthralgias. She was known to have had congenitally hypoplastic nails and patellae. Lumbar lordosis, arthritis, and nail dysplasia have been recognized in this patient, her mother, grandfather and four maternal aunts. Her grandfather had rectal adenocarcinoma in 1945 documented at this institution, and died at age 71. A maternal aunt and her mother also had colon carcinoma. One son has nail and patellar hypoplasia with occasional arthralgias, and other family members have a variety of these manifestations (Fig. 1).

Four years prior to this evaluation, she had a single episode of blood tinged diarrhea. Gastrointestinal work-up demon-

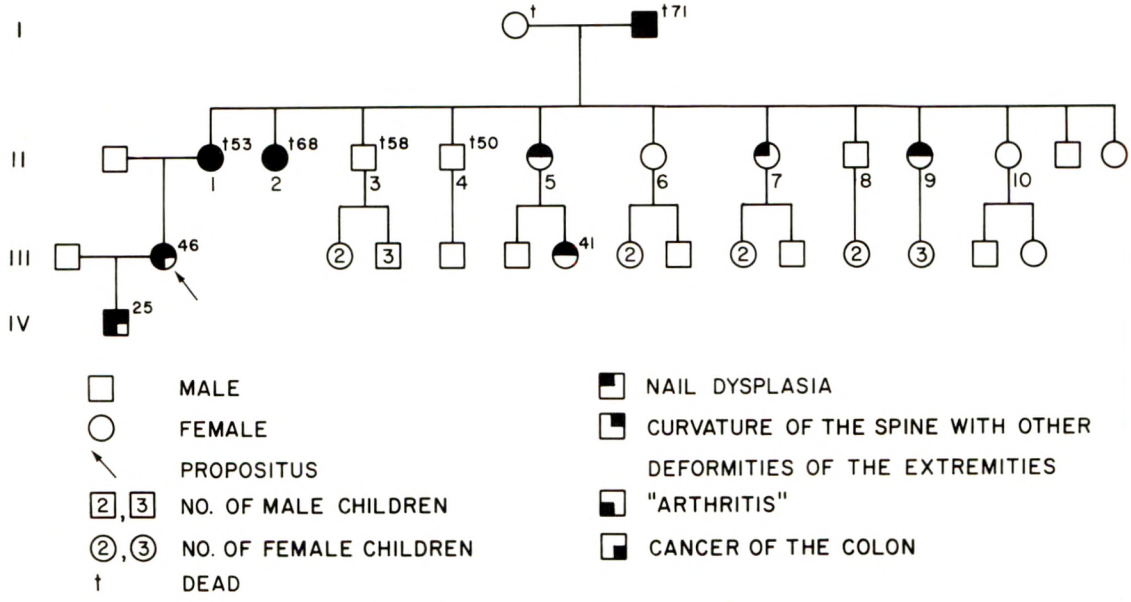

FIG. 1. This pedigree indicates the major familial features.

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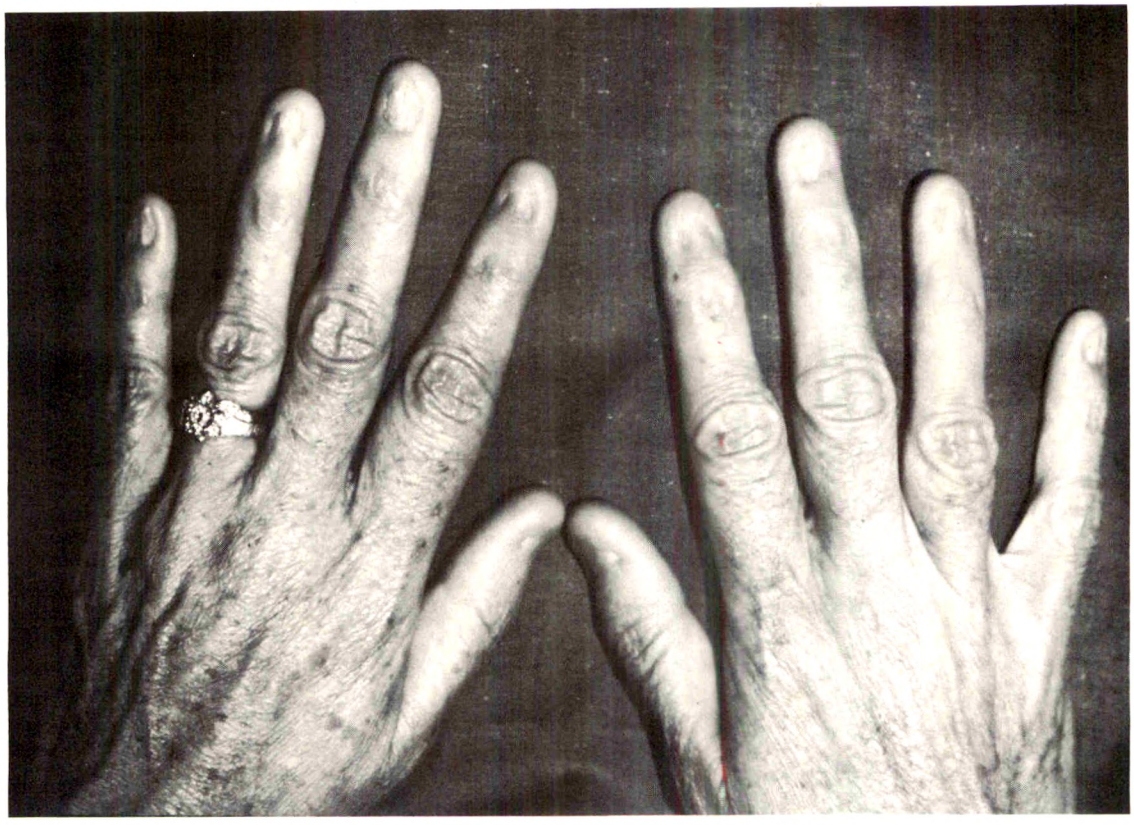

Fig. 2. All the fingernails are strikingly hypoplastic.

strated only irritability of the sigmoid colon, small hemorrhoids, and hiatus hernia. Subsequently, she has had no known recurrence of intestinal bleeding. In the past, she has been treated for "stomach ulcers." Both she and her son have multiple sebaceous cysts, most prominent about the head and neck areas, but have no other features for Gardner's syndrome. One year prior, biopsy of a pruritic skin eruption demonstrated lymphocytic vasculitis of the upper dermis consistent with polymorphic light eruption.

On physical examination, the patient is alert and cooperative, weighs 113 pounds and is 66 inches tall. Her elbows lack 20 degrees of complete extension. Nails on her thumb and index finger are virtually aplastic, and the remainder of her fingernails are aplastic (Fig. 2). All the proximal interphalangeal joints of both hands, especially of the second and third fingers, are tender with synovial thickening. Her distal interphalangeal joints are also tender. The patellae are barely palpable, and her knees are normally mobile without instability. Onychomycosis of the toenails is present. The iliac crests have decreased flaring, and no iliac horns are palpable. Lumbar lordosis is increased. Other aspects of her physical examination are noncontributory except heterochromic iritis.

Routine laboratory work is entirely normal with no clinical or laboratory evidence of renal involvement. Chromosome analysis demonstrates a normal female karyotype. Rheumatoid factor and antibody are not present.

Roentgenographic evaluation demonstrates small bilateral exostoses projecting from the posterior aspect of the iliac crests (Fig. 3, *A* and *B*). Both patellae are hypoplastic (Fig. 4, *A–C*), with the right being smaller than the left. The ventral aspect of

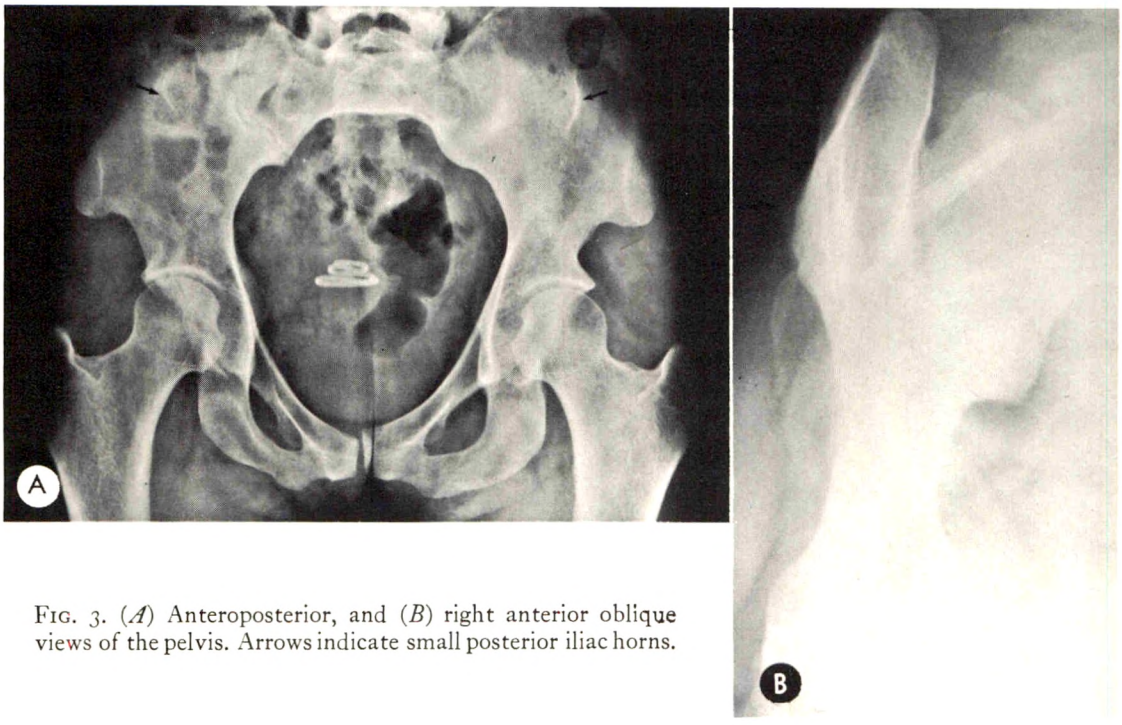

Fig. 3. (*A*) Anteroposterior, and (*B*) right anterior oblique views of the pelvis. Arrows indicate small posterior iliac horns.

both medial femoral condyles is flattened. Her elbows are normal roentgenographically; however, humeral heads and glenoid processes of the scapulae are symmetrically flattened and dysplastic (Fig. 5). The ulnar styloid processes are absent bilaterally. The proximal interphalangeal joints of most fingers have small osteophytes, and the second, third, and fourth proximal interphalangeal joints have capsular swelling. Her fourth and fifth metacarpal bones bilaterally are more gracile than normal (Fig. 6, *A* and *B*).

DISCUSSION

Hereditary onycho-osteodysplasia is comprised of a tetrad of major findings. Nail and patellar hypoplasia or aplasia, dysplastic changes of the elbow, and exostoses or "iliac horns" projecting off the posterior surface of the iliac crest form the complete syndrome. A patient has this syndrome when at least two of these four major findings are present. Fingernails typically of the thumbs, may have any degree of absence, especially medially and distally. Other nail alterations including longitudinal grooves, softening, and discoloration, are present from birth, and affect the fingers far more often than the toes.

Patellar hypoplasia is usually due to absence of its medial portion. The medial and lateral components of the knee joint and patella develop separately, with the medial portion developing first and more rapidly. By the 30 mm. embryonic stage, development of the knee joint is predetermined. In an ill-understood manner the mesenchymal precursor of the vastus medialis muscle and the medial portion of the patella fail to properly differentiate, resulting in its absence. This is felt to be due to a hereditary abnormality.[19] By arthrography, Nickerson[19] demonstrated a persistent vertical midline fibrous or cartilaginous septum in the knee joint of a single patient with nail-patella syndrome. The infrapatellar fat pad and a small exostosis sometimes seen on the tibial articular surface in the midline, anterior to the tibial spines, are remnants of this septum. Associated with the hypoplastic patella may be a flat

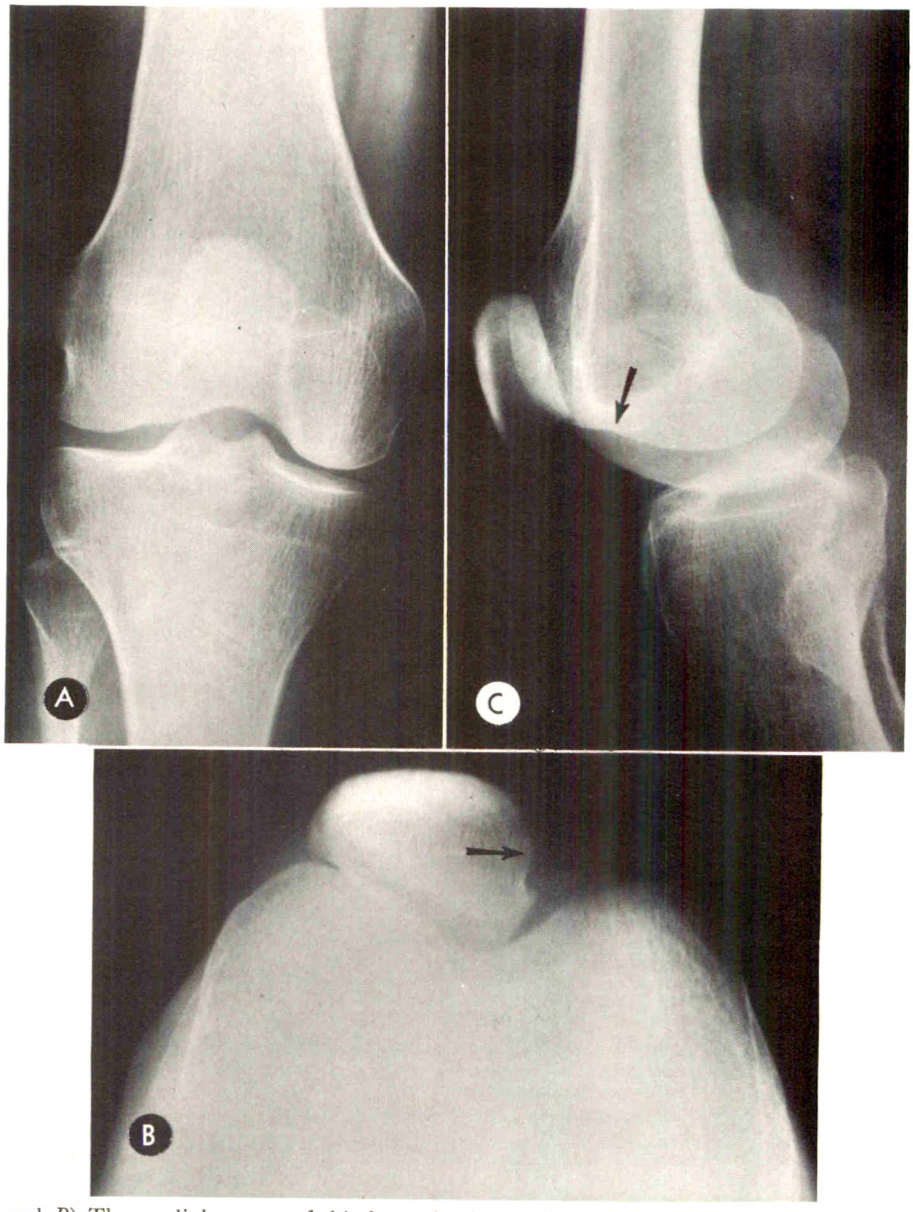

Fig. 4. (*A* and *B*) The medial aspect of this hypoplastic patella is prominently affected (arrow). (*C*) The medial femoral condyle is flattened ventrally. The lateral femoral condyle is identified by a normal concavity in its articular curvature (arrow). The left knee has a similar appearance.

lateral femoral condyle and a prominent medial femoral condyle. The patella usually is located more lateral and higher than normal, and recurrent lateral dislocations may occur.

Dysplastic changes of the elbow include posterior dislocation of a deformed radial head and neck with resultant smaller size of the capitellum and increased prominence of the trochlea. Motion is usually restricted with limitation of supination, pronation and full extension. Exostosis of the proximal ulna pointing toward the radius, and antecubital fossa webbing are also reported.

"Iliac horns"[9] when present are pathognomonic of this condition.[25] They are of variable size, have no function, usually

cause no symptomatic problems, and have not been found in other animals to give a clue as to their developmental function. These exostoses may be found in 30 per cent of patients;[4] 71 per cent are palpable, and 81 per cent are seen on roentgenograms. Nail abnormalities are found in 98 per cent, elbow dysplasia in 90 per cent, and hypoplastic or aplastic patellae occur in 79 per cent of patients.[6] A very large number of other associated skeletal findings have been described by various authors.[4,6,10,13,17,21,22,25] The lack of ulnar styloid processes in this patient has not been previously described, and has been seen by these authors only in one other patient who was seen preoperatively for giant-cell tumor of tendon sheath of the finger, and who did not have nail-patella syndrome. This patient's articular involvement limited to her hands, with definite clinical and roentgenographic findings, is not characteristic of a known type of arthritis. Several members of this family had arthritis (Fig. 1), which was not reported in other cases of nail-patella syndrome.

Renal abnormalities are a well recognized part of this syndrome occurring in as many as 42 per cent of patients in one series,[6] with proteinuria the main finding, and hematuria occasionally occurring. Under light microscopy, findings may suggest a diabetic glomerulosclerosis[17] with some focal glomerular necrosis,[2] but on electron microscopy, changes characteristic for osteo-onychodysplasia may be detected. Increased deposition of collagen fibers with abnormal periodicity may be detected in the basement membrane of glomeruli, as well as slight increase in the mesangial matrix. Swelling of epithelial cells and fusion of foot processes may also be detected on electron microscopy. The opposite changes in mesangial matrix and basement membrane occur in diabetic nephrosclerosis.[3,17] Various degrees of renal involvement are found in skeletally affected family members, with some asymptomatic patients having early changes in glomeruli on electron microscopy and other patients having end stage renal disease and renal osteodystrophy.[3,8]

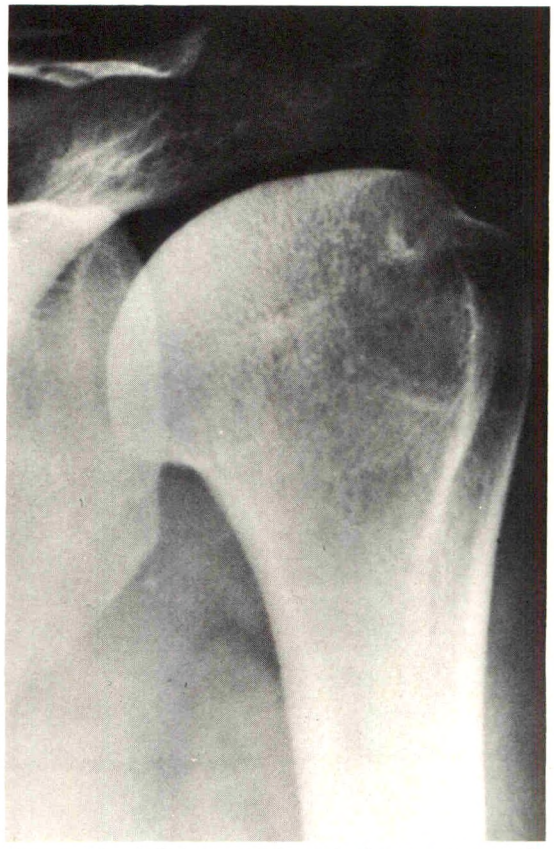

Fig. 5. The left humeral head is flattened, and the glenoid portion of the left scapula is dysplastic. The right shoulder has an identical appearance.

Genetically, the loci for nail-patella syndrome, the ABO blood grouping, and the enzyme adenylate kinase are closely arranged on the short arm of the first chromosome.[23] This close arrangement explains why patients in the same family have the same blood group and the identical form of adenylate kinase. Such an arrangement of three loci is termed a true tripartite genetic linkage.[20] A true linkage is one in which two loci in a single chromosome are sufficiently close that an expression occurs more commonly than expected with random assortment. The syndrome is passed as autosomal dominant with complete penetrance, and occasionally sporadic cases are found. This condition has variable expressivity,

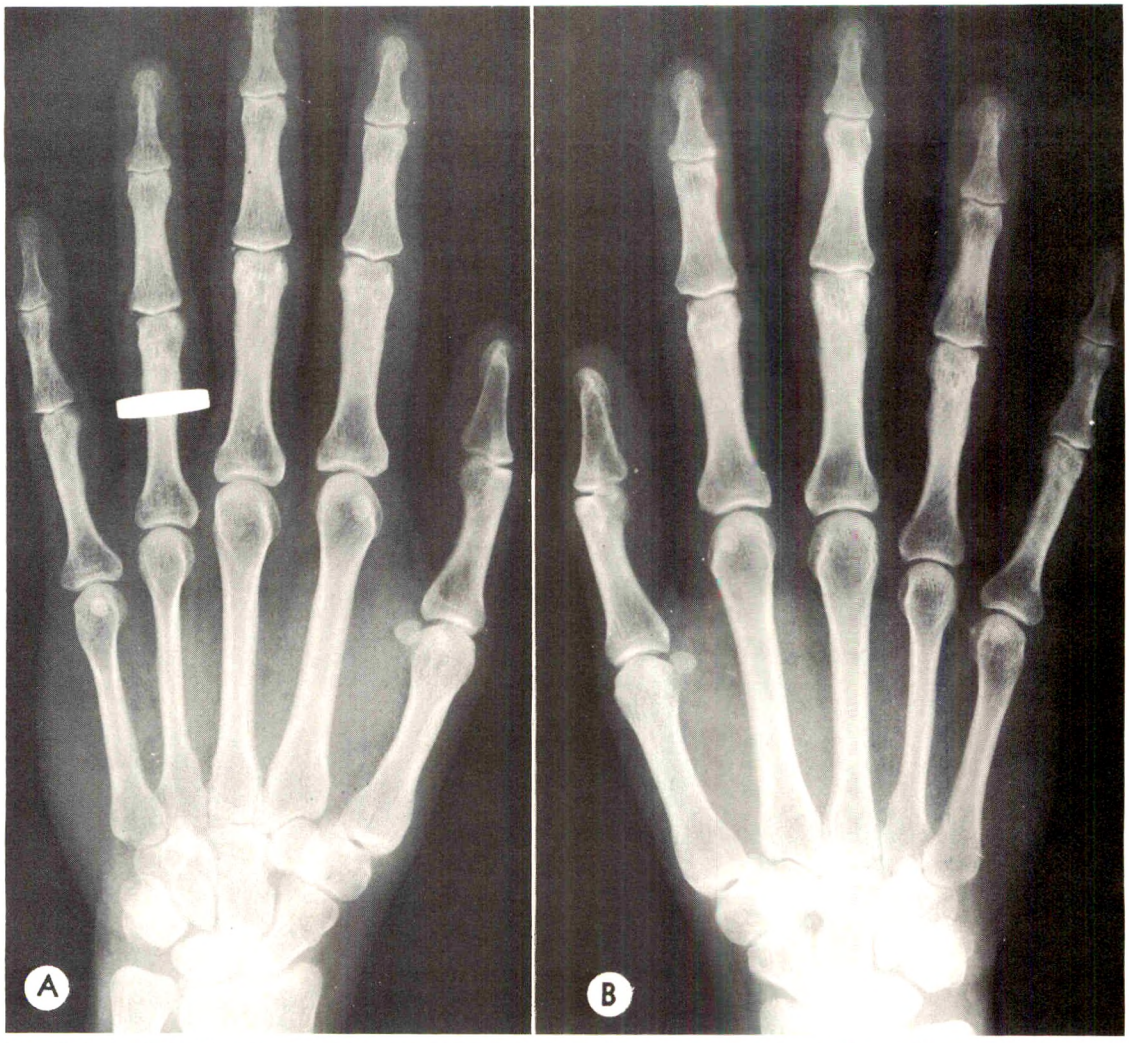

Fig. 6. (*A* and *B*) The ulnar styloid processes are absent. Some proximal interphalangeal joints are narrowed centrally with capsular swelling and associated degenerative spurs and bony ossicles. The fourth and fifth metacarpal bones are gracile.

the gene is pleomorphic,[7] and there is no sex predilection.

An increased incidence of colon carcinoma was not found in other reported families with nail-patella syndrome. With 3.5 cases of colon and rectal carcinoma per 100,000 population reported as a high incidence,[5] the 3 cases in this family represent an abnormally increased occurrence of this tumor. Since many family members are quite young, other cases of colon carcinoma may yet develop. Burkett[5] excellently describes many factors, especially dietary, predisposing to colon carcinoma and precancerous conditions of the colon. The affected family members in this case lived in different areas and were in different generations, and none of the spouses had colon carcinoma; therefore, dietary factors do not appear to be incriminated to explain the colon cancer incidence in this family. Although sebaceous cysts occur in this patient and her son, no osteomas, colonic or rectal polyposis, dentigerous cysts or other changes in her mandible were found on an extensive roentgenologic evaluation. Her

son and none of the other family members have yet displayed findings for Gardner's syndrome. Familial polyposis, Peutz-Jegher's syndrome, solitary polyps, and other conditions having an increased incidence of colon carcinoma[14] were not found here, and the criteria for a "cancer family"[18] are not present in this case. Families have been found[24] with genetic predisposition to form solitary premalignant polyps, not of the familial polyposis type. Here, no polyp formation was found, and it appears probable that this patient's family has genetic predisposition for colon carcinoma. The knowledge that nail-patella syndrome is genetically determined, and that some cases of genetic predisposition for colon carcinoma exist,[15] suggests in this family that these 2 entities belong to the same linkage group.

SUMMARY

A family with nail-patella syndrome having an increased incidence of colon carcinoma has been reported. The possibility exists that colon carcinoma might be a previously undetected component and a part of the linkage of nail-patella syndrome.

The main features of osteo-onychodysplasia are described. Nonspecific arthritis and absent ulnar styloid processes are added to the list of findings associated with this syndrome.

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HEMANGIOMAS OF THE LIVER IN INFANTS*

REVIEW OF DIAGNOSIS, TREATMENT AND COURSE

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CAVERNOUS hemangioma and hemangioendothelioma are the primary benign vascular liver tumors which occur in infancy.[3] Infants with these lesions usually present with one or more of the following: an abdominal mass, a high output cardiac state, or in frank congestive heart failure. The roentgenologic diagnostic approach to these infants should include the use of total body opacification in intravenous pyelography, liver scanning, and angiography.[2,15]

Clinical and roentgenologic findings are presented in 6 infants with benign vascular liver tumors. All had a high cardiac output or were in frank congestive heart failure caused by hepatic arteriovenous shunting.

Although earlier reports had suggested that the detection of a vascular liver tumor in infancy represents a pediatric surgical emergency, favorable experience with the last 4 medically treated cases has led to a reconsideration of the principles of treatment.

MATERIAL

(Table I)

The 6 infants were first seen from Day 1 of life to 3 months of age. A discrete abdominal mass, or enlarging liver was the presenting sign in 4 cases which were seen on Day 1. Frank congestive heart failure was clinically the major problem in 2 of the 6 cases, although all of the patients manifested features of a high cardiac output. Other pertinent physical findings on admission were cutaneous hemangiomas (3), significant cardiac murmurs (4), and an abdominal bruit (1).

DIAGNOSTIC INVESTIGATIONS

(Tables II and III)

The modalities of diagnosis were: (1) intravenous urography with total body opacification; (2) radionuclide evaluation of the liver; (3) umbilical venography; and (4) arteriography, either umbilical or performed as part of cardiac catheterization.

The urographic scout roentgenogram showed either hepatomegaly or a right-sided mass in addition to cardiomegaly. Only 1 patient (Case 1) had hepatic calcifications. Three of the 6 patients showed abnormal liver findings on the total body phase of the intravenous pyelogram.

All 4 patients who had technetium sulfur colloid 99m liver scans showed abnormalities in uptake, ranging from mottling to discrete masses. One patient (Case 6) was also studied with indium 113m; in this case the "cold" spots on the technetium scan were now shown to have uptake, reflecting the vascular nature of the tumor.

Umbilical venograms, performed in 3/6 patients, showed the left lobe of the liver to be normal. In 1 of the 3 there was rapid filling of portal channels within the tumor of the right lobe, with subsequent massive hepatic vein run-off.

The most significant diagnostic test was clearly arteriography, with all 6 infants showing the hypervascular nature of the lesion and early draining hepatic veins.

PATHOLOGY, TREATMENT AND FOLLOW-UP

(Table IV)

Four of 6 patients are alive and well fol-

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TABLE I

CLINICAL PRESENTATION

Case	Sex	Age	Presenting Sign or Symptom	High Output Cardiac State or Congestive Heart Failure	Cutaneous Lesions	Presence of Cardiac Murmur	Abdominal Bruit
1.*	M	1 da.	Abdominal mass, jaundice, petechiae	+	o	+	o
2.*	M	1 da.	Abdominal mass	+	+	o	o
3.	M	5 wk.	Congestive heart failure, failure to thrive	+	+	o	+
4.	F	3 mo.	Congestive heart failure	+	+	+	o
5.	F	1 da.	Enlarging liver	+	o	+	o
6.	F	1 da.	Abdominal mass	+	o	+	o

* Previously reported.[2]

lowing non-surgical treatment. The period of follow-up extends from 3 months to 2 years. The treatment given to these 4 patients includes digitalis, steroids, and radiation therapy, or combinations thereof.

One patient had surgical excision of his right hepatic lesion and 1 patient died of congestive heart failure because of a delay

TABLE II

ROENTGENOGRAPHIC MODALITIES OF DIAGNOSIS

Case	Urography (total body contrast)	Umbilical Venography	Umbilical Aortography	Liver Scan with Technetium 99m
1.	Large lucent area of right lobe of liver	—	+	—
2.	Large lucent area of right lobe of liver	Normal left lobe	+	—
3.	Normal	—	+	Focal defect, right lobe
4.	Normal	—	+	Diffuse abnormalities of both lobes
5.	No early roentgenograms	Normal left lobe communicated with right portal system and large hepatic vein shunting	+	Focal defect, right lobe
6.	Large lucent area of right lobe of liver	Normal left lobe	+	Focal defect, right lobe*

* Had indium 113m liver scan which showed vascularity in these regions of focal defects.

Table III

ANGIOGRAPHIC FINDINGS

Patient	Hepatic Artery	Aortic Size Distal to Hepatic	Hypervascular Lesion	Arterial Neovascularity	Early Draining Hepatic Vein	Shunting to Portal Vein
Case 1.*	*	*	+	+	*	o
Case 2.	Large	Normal	+	+	+	o
Case 3.	Large	Small	+	+	+	o
Case 4.†	Large	Small	+	+	+	o
Case 5.	Large	Small	+	+	+	o
Case 6.	Large	Small	+	+	+	o

* Done as postmortem study.
† Only patient with both lobes involved.

in diagnosis. These 2 patients had the pathologic diagnosis of cavernous hemangioma.

DISCUSSION

LOCALIZATION OF THE LESION

All of the infants who presented on the first day of life had an abdominal mass. As the commonest cause of a neonatal abdominal mass is a multicystic or hydronephrotic kidney, the initial roentgenographic procedure in these patients was intravenous urography (3 ml. of contrast medium per kg.). The kidneys were normal, but during the total body opacification phase of urography, the liver abnormalities became apparent. In infants with vascular liver tumors, the tumor may take up an inordinate amount of contrast medium and give the entire liver a mottled

Table IV

SUMMARY OF PATHOLOGY, TREATMENT AND COURSE

Case	Pathology	Digitalis	Corticosteroids	Radiation Therapy (roentgen)	Surgery	Follow-up	Course
1.	Cavernous hemangioma	+	—	—	—	Died 54 hours	
2.	Cavernous hemangioma	+	—	—	Right hepatic lobectomy	7 years	Well
3.		+	—	450	—	1 year	Well
4.		+	5 mg./kg. prednisone	600	—	2 years	Well
5.		+	10 mg./kg. prednisone	—	—	Lost after 3 months	
6.		+	2 mg./kg. prednisone	150	—	8 months	Well

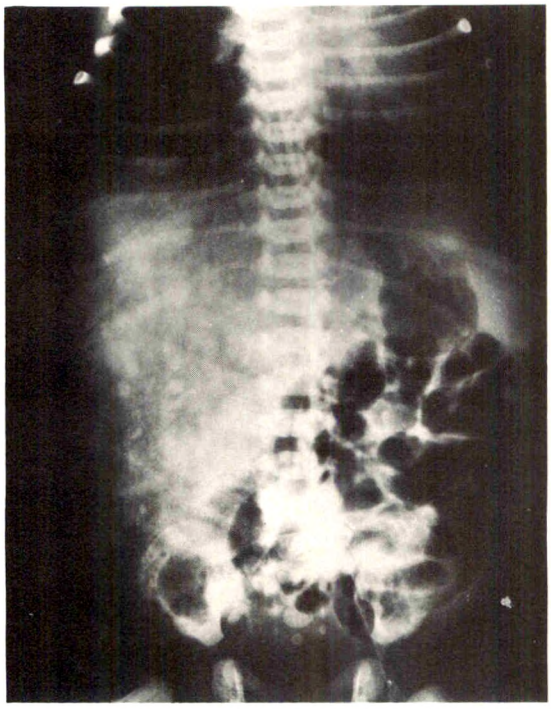

Fig. 1. Case 6. Right abdominal mass palpated. Intravenous pyelogram shows, on "total body opacification phase," mottled collections of contrast medium within the right lobe; kidneys were normal on later studies.

appearance in which areas of focal hemorrhage and/or necrosis appear lucent and the more vascular regions of the tumor appear opaque.[2,18] Three of these patients had an abnormal total body opacification phase demonstrated within the liver (Fig. 1). In the fourth patient (Case 5) early roentgenograms were not obtained. Thus, the diagnosis of a vascular liver tumor could be made on urography in 3 of our 6 patients.

In the 2 patients presenting with frank high output congestive failure, suspicion focused on a congenital heart lesion and cardiac catheterization was undertaken. Since cardiomegaly and murmurs may occur in infants with intra- or extracardiac causes of congestive failure, the findings of a large liver out of proportion to the degree of failure, an abdominal bruit, and cutaneous hemangiomas are helpful when present. Unfortunately, they are frequently absent (Table 1). Because of the paucity of clinical findings in patients with vascular liver tumors, the patient in congestive heart failure who comes to cardiac catheterization should be investigated for hepatic and central nervous system arteriovenous shunts if no cardiac lesion accounting for the failure is readily apparent. A left ventricular or an aortic root injection with films centering on the abdomen must be done to confirm the hepatic tumor (Fig. 2, *A–C*; and 3, *A–C*).

DEFINING THE LESION

Once the lesion has been localized to the liver, the diagnostic problem is somewhat different. First, the extent of the tumor (and normal liver) must be defined. The 2 roentgenographic studies which help define the normal liver are the liver scan and the umbilical venogram. In 3 of the 4 patients studied with technetium 99m sulfur colloid, focal defects were detected only in the right lobe and the left lobe appeared normal. On the fourth patient there were diffuse abnormalities of both right and left lobes. In addition, this non-invasive, low radiation exposure technique provides an optimal roentgenographic mode of follow-up. For this reason, all patients should have a baseline liver scan.

The second roentgenographic mode of defining the normal liver is umbilical venography. This can demonstrate the normal hepatic parenchyma, as 75 per cent of the normal hepatic blood flow is via the portal vein. Since the umbilical vein enters the left portal vein, however, only the left lobe of the liver may be seen, as was demonstrated in 2 of the 3 patients studied (Fig. 4*A*). In the third patient, a normal left lobe was seen but there was also reflux into the right portal system (Fig. 4*B*). Contrast material was seen entering the tumor and shunting rapidly into an hepatic vein. It is worth reiterating that the portal vein supplied the blood flow to the normal liver while an enlarged hepatic artery supplied most of the blood flow to the vascular tumor. It is for this reason that arteriog-

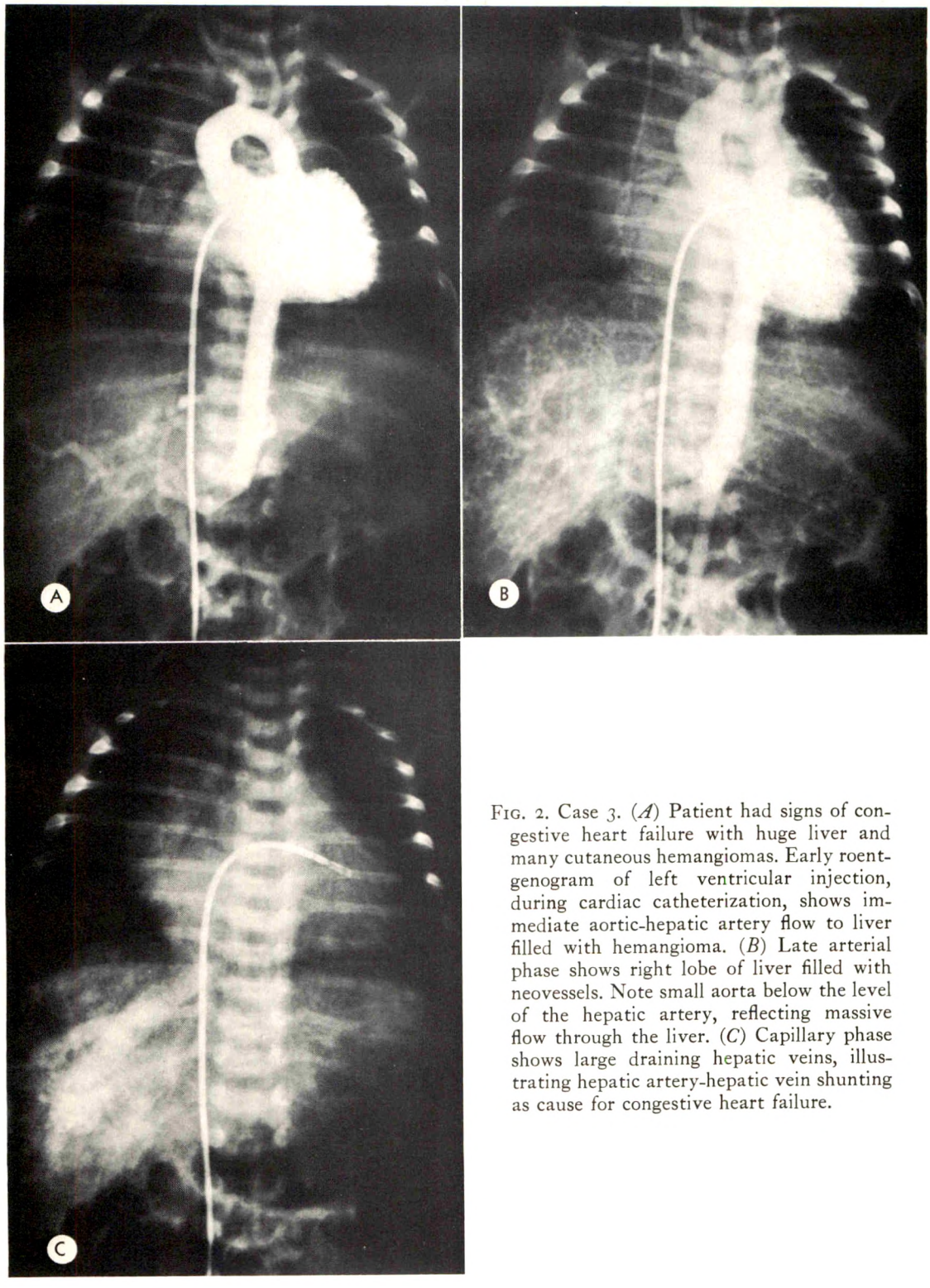

Fig. 2. Case 3. (*A*) Patient had signs of congestive heart failure with huge liver and many cutaneous hemangiomas. Early roentgenogram of left ventricular injection, during cardiac catheterization, shows immediate aortic-hepatic artery flow to liver filled with hemangioma. (*B*) Late arterial phase shows right lobe of liver filled with neovessels. Note small aorta below the level of the hepatic artery, reflecting massive flow through the liver. (*C*) Capillary phase shows large draining hepatic veins, illustrating hepatic artery-hepatic vein shunting as cause for congestive heart failure.

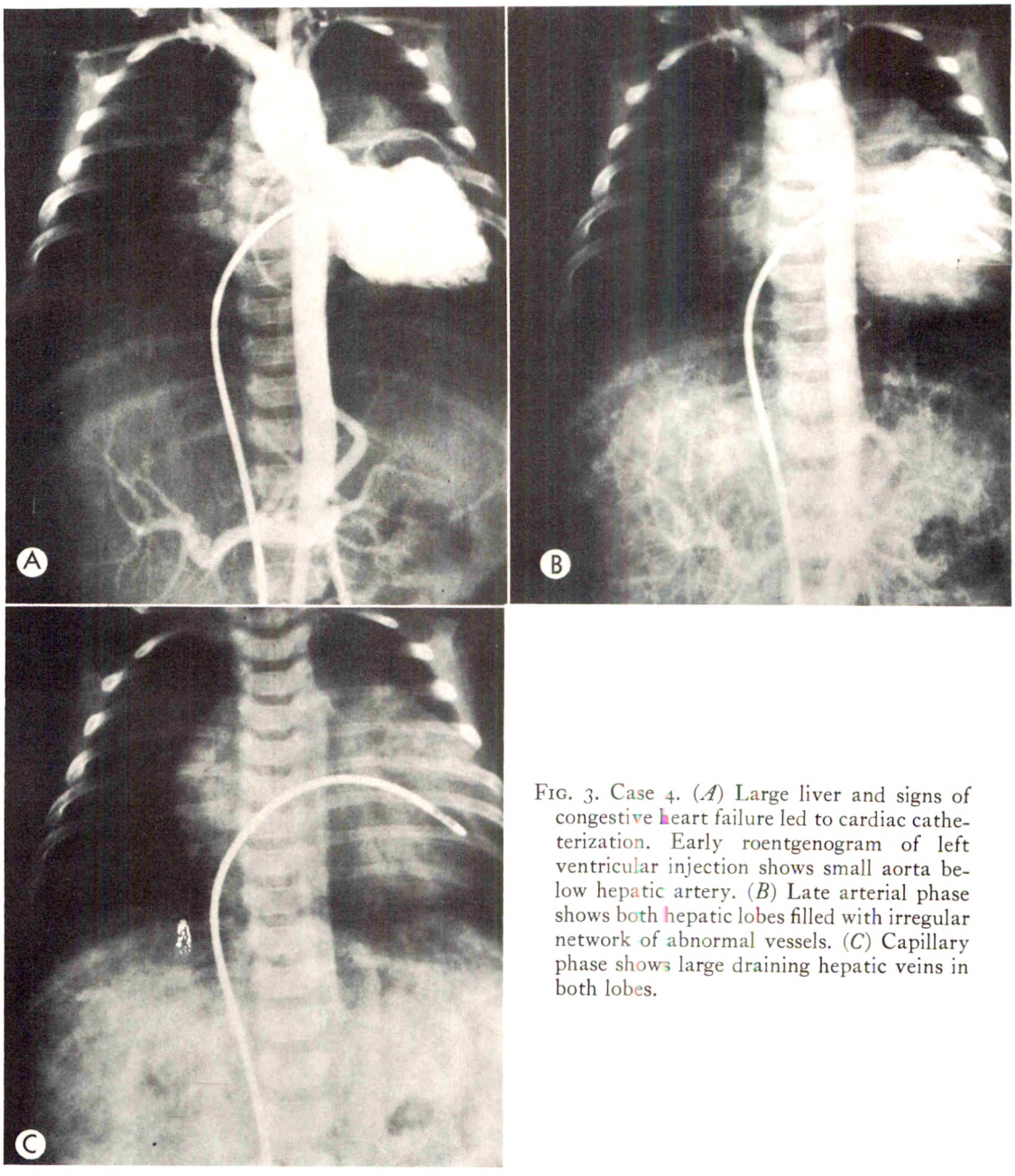

Fig. 3. Case 4. (*A*) Large liver and signs of congestive heart failure led to cardiac catheterization. Early roentgenogram of left ventricular injection shows small aorta below hepatic artery. (*B*) Late arterial phase shows both hepatic lobes filled with irregular network of abnormal vessels. (*C*) Capillary phase shows large draining hepatic veins in both lobes.

raphy should be utilized to define the extent of the tumor and the blood supply to the tumor in the eventuality of surgical excision, and venography used to show the normal liver. Because these lesions are hypervascular, the feeding artery is dramatically enlarged (Table III; Fig. 2*A*; and 3*A*). The aorta distal to the feeding artery (the superior mesenteric artery or celiac artery) markedly diminishes in size (Fig. 2*B*; and 3*A*). The presence of the enlarged feeding artery, hypervascularity of the lesions, and the early draining hepatic veins (Fig. 2*C*; and 3*C*) readily explains the pathophysiology of the high output state.

Additional and important angiographic

findings were neovascularity (6 of 6) and large vascular lakes with pooling (3 of 5). The degree of neovascularity varied from a fine diffuse pattern resembling a hepatoma (Case 3; Fig. 2*B*) to those with both neovascularity and persistence of vascular lakes of contrast medium as the predominant findings (Case 6; Fig. 5, *A* and *B*). Those with the dilated vascular lakes were precisely those individuals having large lucent areas on the total body opacification phase of the intravenous pyelogram (Cases 2 and 6; Fig. 1).

It has been shown that rapid shunting of blood through an arteriovenous fistula or hemangioma may produce an increase in heart size due to cardiac hypertrophy and dilatation, necessary for increased stroke volume.[10] In these compensated individuals the cardiac output is increased, the blood volume is increased, and the response to digitalis is negligible. However, after a period of stress, there is true myocardial failure as the cardiac output drops, circulation time is increased, and the response to digitalis may be gratifying.[10]

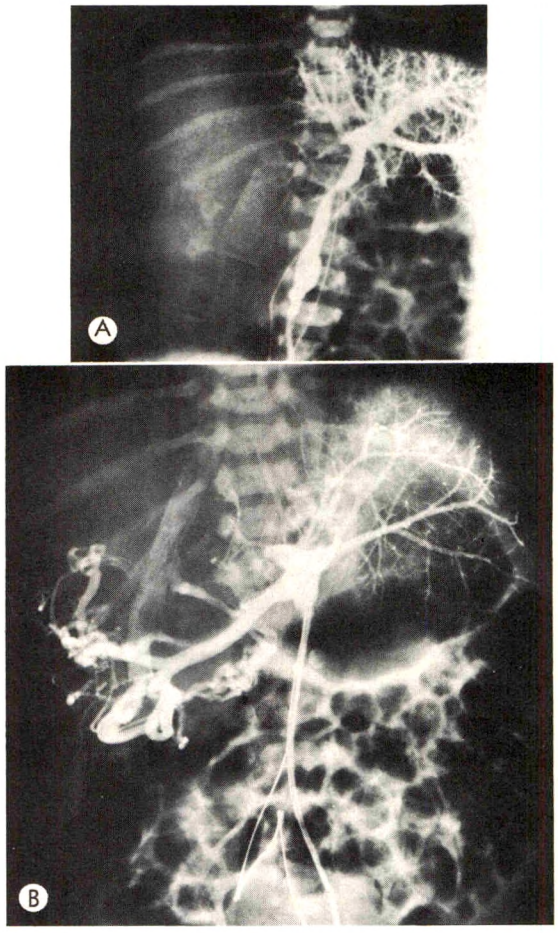

Fig. 4. Case 6. Intravenous pyelography on this patient had shown right hepatic vascular mass (see Figure 1). (*A*) Umbilical venogram shows normal left hepatic parenchyma without evidence of extension of tumor into left lobe. (*B*) Case 5. Patient had right hepatic hemangioma. Umbilical venogram shows normal left lobe; in addition there is right portal flow through hemangioma with filling of huge draining hepatic vein. Thus, this patient had both hepatic artery-hepatic vein and portal vein shunting.

Is the tumor benign or malignant?

All of these findings (hypervascularity, neovascularity, arteriovenous shunting, and pooling) (Fig. 2*B*; and 5*A*), if seen in an adult, are used as signs of malignant liver tumors.[1,16,19] Therefore, additional criteria for the differentiation of benign from malignant hepatic lesions in children must be utilized.[17]

Aside from the primary benign vascular tumors, the major diagnostic consideration is an hepatoblastoma. However, the clinical finding of congestive heart failure and the angiographic finding of early draining hepatic veins (Fig. 2*C*; 3*C*; and 5*B*) point convincingly to a benign primary vascular tumor of the liver, since this combination of findings has not been seen to date with hepatoblastoma.[5,13]

Treatment

The natural history of benign primary vascular liver tumors in children is regression. Therefore, supportive therapy is the primary mode of management and digitalis, corticosteroids and radiation therapy have been utilized in this regard.[6] In addition, 2 modes of surgery have been entertained—excision of the lesion, or hepatic artery ligation.[4,11]

All of our patients were digitalized because it was difficult clinically to distinguish between high output cardiac state and the early signs of myocardial decom-

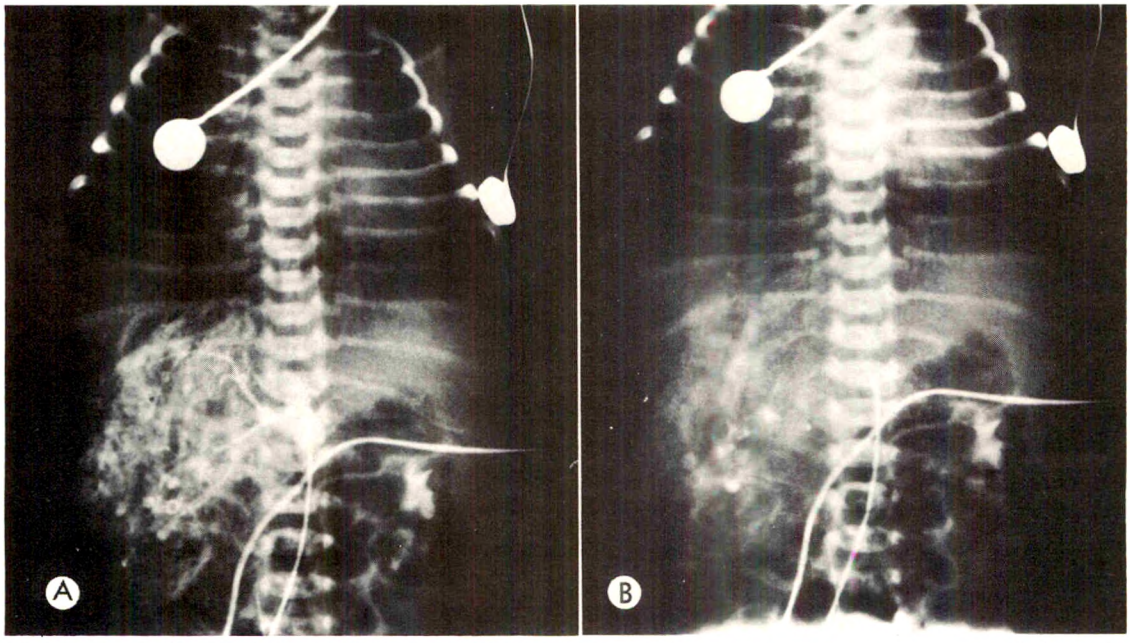

Fig. 5. Case 6. (See Figure 1 for urogram and Figure 4*A* for umbilical venogram on same patient.) (*A*) Umbilical aortogram shows lack of filling of the aorta as all of contrast medium went into the right hepatic vascular tumor mass. (*B*) Capillary phase shows both persistence of contrast material in vascular lakes as well as large early draining hepatic veins.

pensation.[10] Since none of the patients were treated with digitalis alone, the efficacy of this treatment was difficult to ascertain. One patient had steroids in conjunction with digitalis (Case 5). A similar case has been described by Goldberg and Fonkalsrud.[6] In both patients the response to corticosteroids was evident within 1 week. as manifest by decreasing liver size and decreasing pulse rate. The cardiac failure became more manageable and the steroids were reduced at 3 weeks. The exact mechanism of the action of steroids is unknown.

One patient was treated with digitalis and radiation therapy (Case 3). A total of 450 rads was delivered in 3 treatments, using a cobalt 60 source. The patient did well with regression of the size of the tumor within 4 days.

Two patients were treated with digitalis, steroids and radiation therapy (Cases 4 and 6). Case 4, who had hemangiomas in both right and left lobes of the liver, did not respond to digitalis and corticosteroids over a 2 month period, and only after this trial was she given radiation therapy. Gradually her signs and symptoms regressed. Case 6 received radiation therapy simultaneously with the administration of digitalis and corticosteroids. She had a dramatic decrease in liver size and decreasing cardiac failure within 3 days.

The specific role of radiation therapy is thus difficult to evaluate because each of the patients received different dosages (Table IV). In addition, although all of the doses were small, the effect of even a small amount of irradiation on the newborn liver has not been adequately evaluated.[20] None of the patients who were treated with irradiation developed clinical radiation hepatitis.

Only 1 patient in our series (Case 2) underwent surgery. This patient had a successful right hepatectomy. Hepatic artery ligation was not performed in any of our patients. It has been shown that the hepatic artery is not an end-artery, and in adults undergoing hepatic artery ligation, the hepatic artery flow was reconstituted distal to the ligature as early as 10 hours after interruption.[12] It appears that any

effect from hepatic artery ligation will indeed be short-lived.

These observations suggest that surgery be reserved for those cases of intractable congestive heart failure, severe unremitting platelet trapping, and rupture of the liver. While the medical therapy was not dramatic in the majority of cases, the patients remained stable and slowly improved. Whether this was because of the natural regression of the vascular lesion or because of the treatment is not known.

FOLLOW-UP AND COURSE

Five of the 6 infants are alive 3 months to 7 years after the diagnosis was made. The 1 patient that died represented a delay in diagnosis and treatment. Although only Cases 1 and 2 had pathologic diagnoses (cavernous hemangiomas), the similarity of clinical presentation, angiographic findings, and course, allows us to classify all of these patients as having benign primary vascular liver tumors. This favorable course is most impressive, as opposed to the grim prognosis of patients with hepatoblastoma who usually die within 1 year after presentation.[8] The survival of a child with an unresected hepatoblastoma beyond this period should prompt one to re-evaluate the biopsy evidence. Indeed, the only reported case of such a spontaneous regression of a malignant liver tumor was reviewed by McSweeney *et al.*[14] 25 years after the initial diagnosis. Both the clinical course and review of the biopsy prompted reclassification of this lesion to that of a primary benign vascular tumor (hemangioendothelioma).

DIAGNOSIS, WORK-UP AND TREATMENT

(Table v)

The diagnostic and therapeutic approach to infants with vascular liver tumors are summarized in Table v. Those infants who presented with an abdominal

Table V

DIAGNOSTIC AND THERAPEUTIC APPROACH TO INFANTS WITH VASCULAR LIVER TUMORS

Presenting Sign	Abdominal mass and/or	High output state or frank congestive heart failure
Localizing the Lesion	Intravenous urogram with "total body opacification"	Angiography
Defining the Extent of the Lesion	Umbilical venography, technetium 99m liver scan, angiography	Technetium 99m liver scan
	High output state with angiogram showing early draining hepatic vein	Neither high output state nor early draining hepatic veins
Diagnosis	Benign vascular liver tumor	? Hepatoma
Therapy	Supportive	Surgery for diagnosis

mass had intravenous urography with total body opacification technique. If an abnormal liver was noted, the patient received a technetium 99m liver scan and umbilical venogram, as well as an angiogram. In those patients who presented in congestive heart failure, angiography localized the lesion. Technetium scans were obtained later. If a child is found to have a vascular liver tumor and is not in the high output cardiac state nor has early draining hepatic veins on the angiogram, the diagnosis of hepatoblastoma must be strongly considered. It is these individuals who should have surgery for a tissue diagnosis.

In those infants with congestive heart failure and early draining hepatic veins on the angiogram, the diagnosis is that of a benign primary vascular liver tumor and supportive therapy is recommended. If, however, intractable congestive heart failure or unremitting platelet sequestration ensues, surgical treatment may be needed. Hepatic rupture is an obvious indication for surgery.

CONCLUSIONS

1. Benign primary vascular liver tumors in infants can present as an abdominal mass or as a high output cardiac state.

2. Total body opacification on the intravenous urogram is the first roentgenographic study utilized in those infants who present with an abdominal mass. Large lucent regions within the liver localize the tumor.

3. Angiography may be the first roentgenographic modality used in those infants presenting in the high output cardiac state. If no lesion accounting for the failure is readily apparent, the patient should be investigated for hepatic and central nervous system arteriovenous shunts.

4. Both the technetium liver scan and umbilical venography are utilized to define the normal liver tissue.

5. Infants with congestive heart failure or in the high output state in whom early draining hepatic veins are seen at arteriography have benign vascular liver tumors, and supportive therapy is initially indicated; indications for surgery are discussed.

6. Infants not in the high output cardiac state, or with congestive heart failure, and without early draining hepatic veins on the arteriogram, should have a tissue diagnosis to rule out an hepatoblastoma.

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ADVERSE REACTIONS TO INTRAVENOUS PYELOGRAPHY IN CHILDREN*

By CHARLES A. GOODING, M.D.,† WALTER E. BERDON, M.D.,‡ ARMAND E. BRODEUR, M.D.,§ *and* MARSHALL ROWEN, M.D.‖

A PROSPECTIVE study was recently undertaken to determine the incidence of adverse reactions to intravenous urography in children.

MATERIAL AND METHOD

A data collection sheet, devised by the authors, was distributed to each member of the Society for Pediatric Radiology. They were asked to record pertinent data regarding intravenous pyelography performed in their hospitals for a 3 month period. The information requested included: total number of pyelograms obtained; total number of patients with adverse reactions; ages and sex of the patients having reactions; whether premedication was used; whether the patients were dehydrated; the type and amount of contrast material used; specific type of major or minor adverse reactions; outcome; whether informed consent was obtained and if so in what manner.

RESULTS

Responses were obtained from 51 hospitals, where a total of 12,419 children had intravenous pyelograms. Of these children, 421 (3.4 per cent) had an adverse reaction to the procedure. The age distribution of children having a reaction was:

newborn to 1 year	13
1 to 3 years	24
3 to 5 years	55
5 to 10 years	144
10 to 20 years	143
not stated	42
Total	421

The sex distribution of patients having reactions was:

boys	181
girls	188
not stated	52
Total	421

In most of these cases, premedication was not used:

premedication	8
no premedication	403
not stated	10
Total	421

Generally these patients were not dehydrated before the examination:

dehydrated	32
not dehydrated	384
not stated	5
Total	421

A test dose of contrast material was not usually administered:

test dose	43
no test dose	373
not stated	5
Total	421

The contrast media used for these examinations were:

Hypaque	266
Renografin	94
Conray 60	34
other	22
not stated	5
Total	421

The adverse reactions were to be described as major or minor in nature. Major reactions include shock, cardiac arrest,

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apnea, asthma, laryngeal edema, anuria, seizures, and death. Minor reactions include nausea, vomiting, urticaria, flushing, and pain.

Major reactions occurred in a total of 5 children, 2 of whom each exhibited 2 major reactions:

laryngeal edema	1
shock	2
asthma	4

The 5 children having major reactions ranged from $4\frac{1}{2}$ to 12 years of age (3 were 10 years old). None received premedication. Only 1 was known to have had a test dose of contrast medium. One child was dehydrated before the examination. The contrast material employed for all 5 children was Hypaque. All 5 children recovered.

Six hundred and seventy-five minor reactions occurred:

nausea	222
vomiting	254
urticaria	80
flushing	56
pain	9
other	53
not stated	1
Total	675

Nausea and vomiting comprised 70 per cent of the minor reactions, and about three-fourths of the patients who experienced nausea and vomiting were more than 5 years of age. Nausea and vomiting may occur as a psychologic reaction to any injection procedure.[9] On the other hand, these 2 reactions may be related to rate of injection. Urticaria was most likely a drug-related phenomenon.

Only 15 (29 per cent) of the 51 hospitals stated that the procedure is performed with informed consent:

consent		15
verbal	4	
written	11	
special form	8	
note in chart	7	
no consent		30
not stated		6
Total		51

DISCUSSION

The over-all incidence of reactions, both major and minor, was 3.4 per cent. This is less than that reported by Witten *et al.*[10] from the Mayo Clinic (7 per cent) or Ansell[1] from Liverpool (8.5 per cent). Any over-all comparison of reaction incidence is difficult because criteria for reactions vary,[1–4] especially for minor reactions.

Age does not appear to be a factor influencing reactions in a pediatric population. None of the patients having major reactions had premedication. The study did not determine what per cent of all patients having urography had premedication. Ansell[1] concluded that antihistamines helped prevent minor reactions but not serious ones, and believed that steroids should be restricted to treatment of all severe reactions.

Only 1 patient having a severe reaction was reported to have had a previous test dose of contrast material. Other investigators[8,12] have concluded that a test dose was of no value in predicting which patients would react and believed that the test dose, in itself, was hazardous.

Previously, dehydration was considered to be a factor influencing reactions to contrast media.[3,6,7] Our data show that major reactions were not related to dehydration, thereby excluding that as a significant consideration.

All 5 major reactions occurred in children who received Hypaque as the contrast medium. In studies on adult populations[1,5,10] no significant difference was found when contrast media were compared. Ansell[1] concluded that asthma-type reactions were more common with methylglucamine than with sodium salts.

No deaths were reported in our study. In the Mayo Clinic series, the mortality rate was 1 in 33,000 and in the Liverpool series 1 in 40,000. One patient in our series died a few days after having had an intravenous pyelogram, but the child had been severely ill with diarrhea, dehydration, and electrolyte imbalance. The radiologist who brought this case to our attention provided

us with the full clinical summary and his conclusion, with which we agree, was that "the death was not a contrast reaction." The renal pathology at autopsy related to disseminated intravascular coagulation or a sequela of prolonged dehydration.

Less than one-third of the hospitals surveyed now obtain informed consent to perform the procedure. The low reaction rate demonstrated by this study (1 reaction/1,780 pyelograms obtained, or 1 patient showing reaction/2,483 pyelograms obtained) would indicate that formalized informed consent procedures are not necessary for this relatively common and generally innocuous procedure.

SUMMARY

In 51 institutions 12,419 intravenous pyelograms were made in children in a 3 month period. Five patients had major reactions (laryngeal edema, shock, asthma, or a combination of these). No deaths resulted from the procedure. A test dose of contrast material was not helpful in predicting adverse reactions. The very low incidence of significant reactions suggests that detailed, informed consent procedures are unjustified.

The Society for Pediatric Radiology adopted our conclusions that intravenous pyelography performed in children has a very low adverse reaction rate and that formalized informed consent is not necessary for this relatively common and generally innocuous procedure.

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THE KNIEST SYNDROME*

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IN 1952, Wilhelm Kniest described a $3\frac{1}{2}$ year old girl with an unusual form of disproportionate dwarfism which he called an "atypical chondrodystrophy."[1]

As the result of a collaborative effort, we have had the opportunity to examine the clinical features, skeletal roentgenograms and chondro-osseous pathology of 12 patients similar to the case described by Kniest. This disorder appears to be a distinct chondrodystrophy which has been named the "Kniest Syndrome."[3–4, 9]

In examining the roentgenograms of these 12 patients from birth to 21 years, we are convinced that one is able to establish the roentgen diagnosis of the Kniest syndrome and to separate this entity from metatropic dwarfism and the spondyloepiphyseal dysplasias with which it has been previously confused.

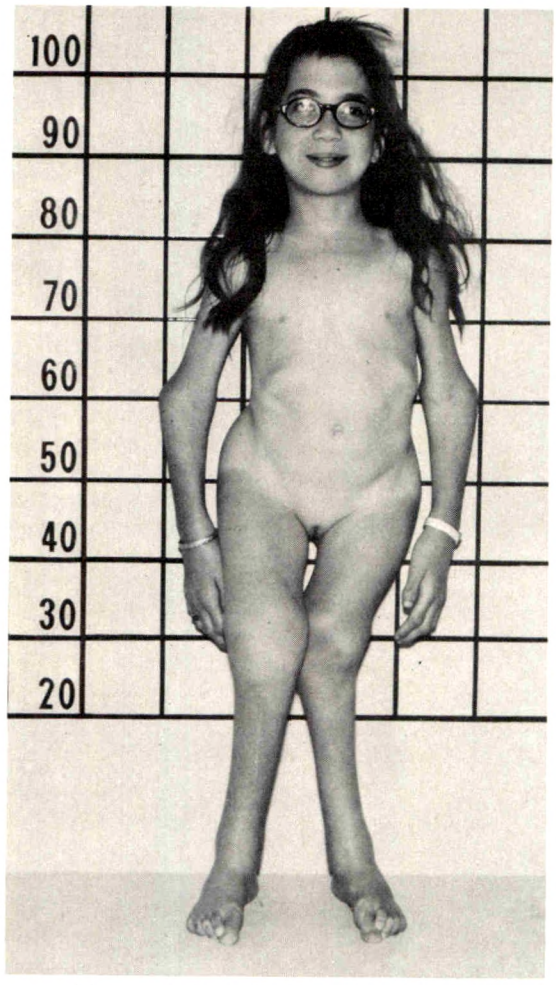

FIG. 1. N.P. A 13 year old with the typical features of Kniest Syndrome.

CLINICAL FEATURES

The clinical presentation of the Kniest syndrome is striking, with disproportionate dwarfism, a shortened kyphotic trunk, deformed extremities with limited joint motion, and a characteristic round, flattened facies (Fig. 1). The diagnosis may be made at birth, because of the deformity of the limbs and enlarged joints. Short stature is moderate in infancy, but becomes significant by early childhood. The joints appear enlarged, especially at the knees, and there is limited motion at all of the major joints with a fixed flexion deformity at the knees and elbows. There is a waddling gait. The fingers appear long and knobby and there is limited flexion at the metacarpophalangeal and proximal interphalangeal joints resulting in the inability to form a fist. The feet are flat and out-turned. The chest appears short, wide, and barrel shaped and there is a prominent dorsal kyphosis. The facies is characteristic, being round and

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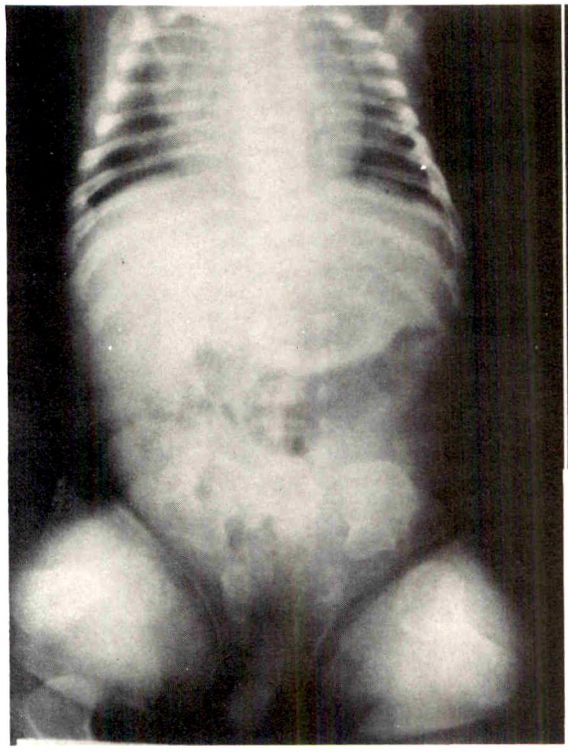


Fig. 2. The newborn pelvis reveals small iliac bones, increased acetabular angles with notching at their lateral margins.

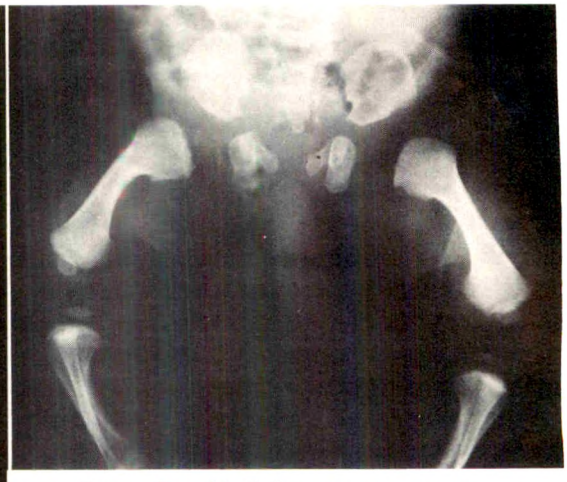
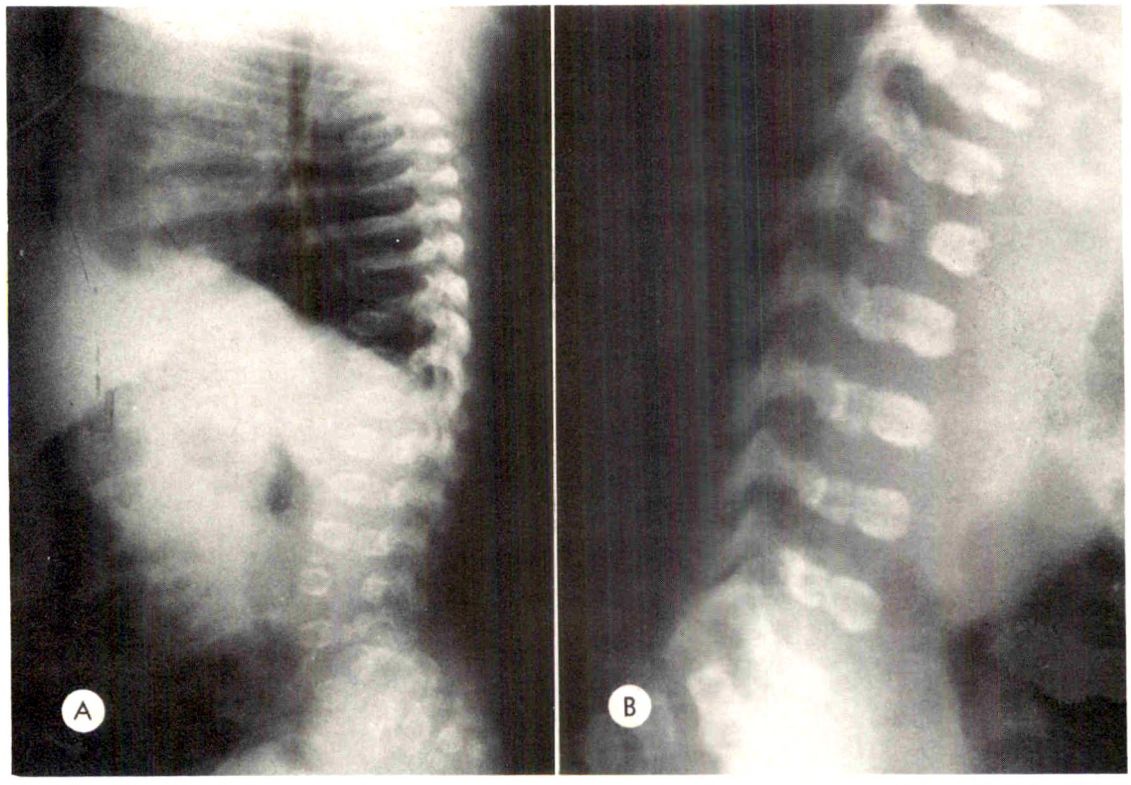


Fig. 3. Dumbbell femora are present.

flattened with a flat wide nasal bridge, prominent eyes and broad mouth. Myopia is frequently severe and may lead to retinal detachment and loss of vision. Cleft palate, hearing loss, recurrent respiratory infections and recurrent otitis media are also frequently present. Motor milestones may be delayed in some patients, but intelligence is usually normal.



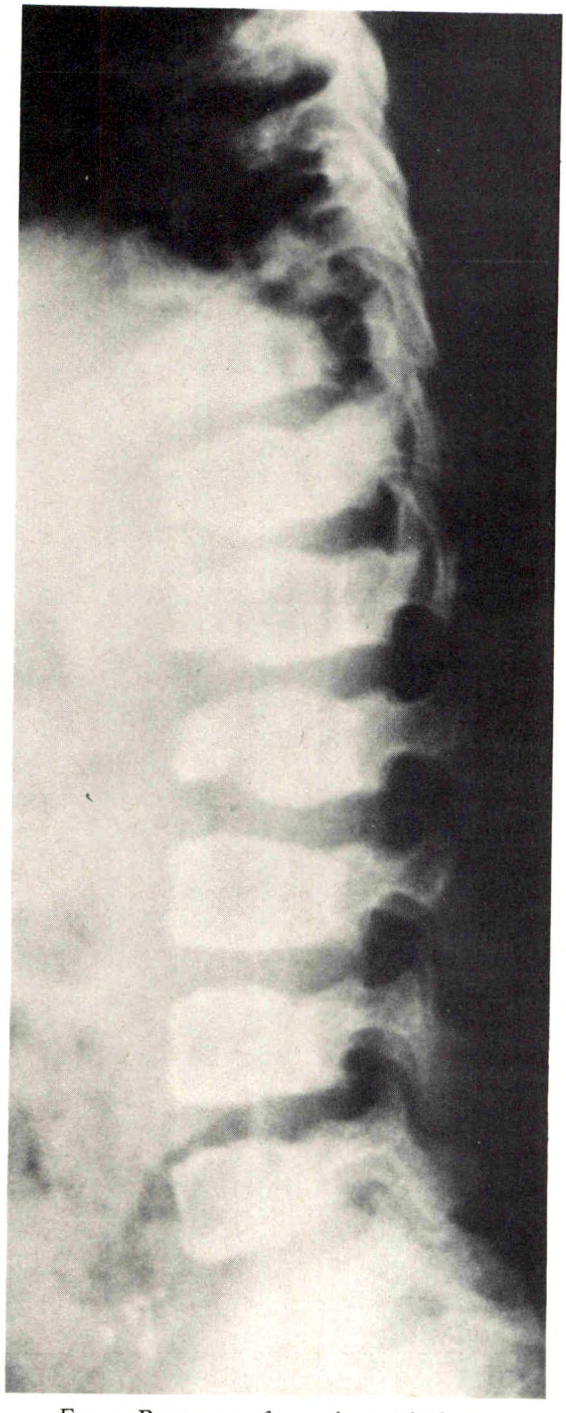


Fig. 5. By 1 year of age, the vertical defects have filled in.

←

Fig. 4. (*A* and *B*) Platyspondyly is apparent, as well as vertical clefts, in the lumbar spine of 2 different infants.

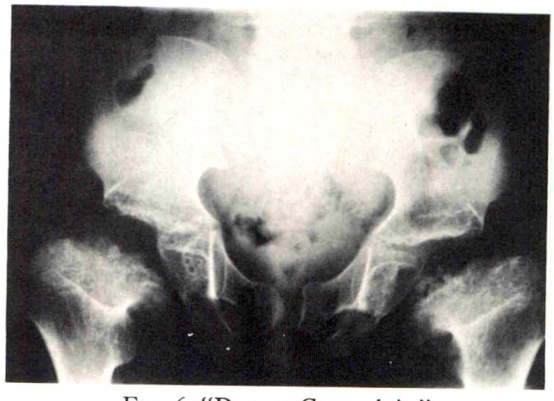


Fig. 6. "Dessert Cup pelvis."

ROENTGENOGRAPHIC FEATURES

Many of these 12 patients have had multiple skeletal surveys at varying ages. We have compared 7 sets of films in the newborn to 1 year of age period; 7 sets from 2 to 5 years; and 4 sets from 6 to 8 years. There were 2 patients with a set of films at 12 years of age, and 1 adult who was 21 years of age. The following roentgenographic descriptions are based upon these combined observations.

During the newborn period, the pelvis reveals diffusely small iliac bones and slightly narrow sacrosciatic notches. The acetabular angles are increased with notching at their lateroinferior margins. Ossification of pubic rami varies from poor to absent (Fig. 2). The femora are dumbbell shaped with expanded ends both proximally and distally, while their diaphyses are

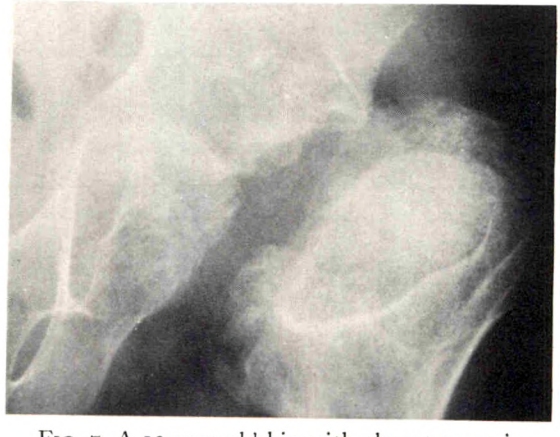


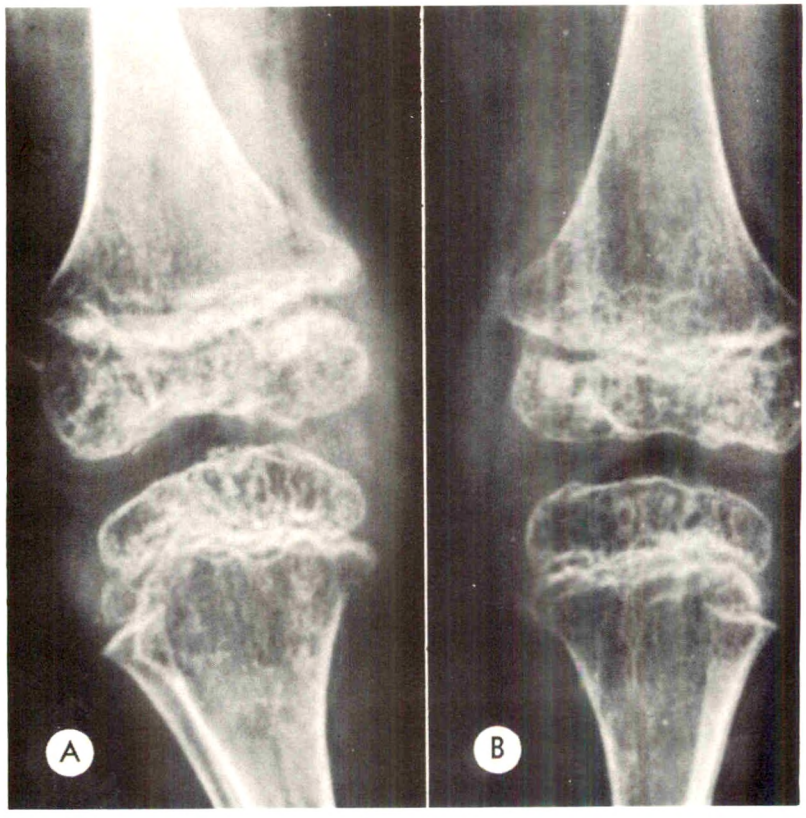
Fig. 7. A 12 year old hip with almost no ossification of the capital femoral epiphysis.

FIG. 8. A hip arthrogram of the same hip as in Figure 7, showing the poorly formed anlage of the femoral head.

shortened. Similar changes are present in tibiae and humeri, producing rhizomelic shortening. Epiphyseal development at the knees is usually radiographically discernible (Fig. 3). The newborn spine shows platyspondyly and verticle clefts are present in the posterior portion of the bodies (Fig. 4, *A* and *B*).

By 1 year of age, the capital femoral epiphyses are not ossified, and most other epiphyseal ossification is quite delayed. The platyspondyly is unchanged, but there is some filling in of the vertebral defects with normal appearing osseous tissue (Fig. 5). By this time, the interpedicular distances of the lower lumbar-sacral area may be slightly narrowed. Some scoliosis is now apparent. The pubis remains hypoplastic.

Because more roentgenograms are available during the postinfancy period into childhood and adolescence and for the sake of continuity, the roentgenographic features will be discussed by anatomic location.



THE PELVIC AREA

By 3 years of age, the pelvis has changed somewhat with flat and very poorly formed acetabular roofs. A decreased pelvic inlet produces, with the pubic hypoplasia, a characteristic "dessert cup" pelvis.

At 6 years of age, there is a similar pelvis with the same hypoplastic down-slanted pubic bones. Femoral ossification is still not present. Peculiar flocculent calcification begins to occur in the metaphyseal regions (Fig. 6). At 12 years of age, the pelvis is unchanged. Small ossified femoral heads may appear roentgenographically in late adolescence. The adult with the syndrome has a slightly more normal appear-

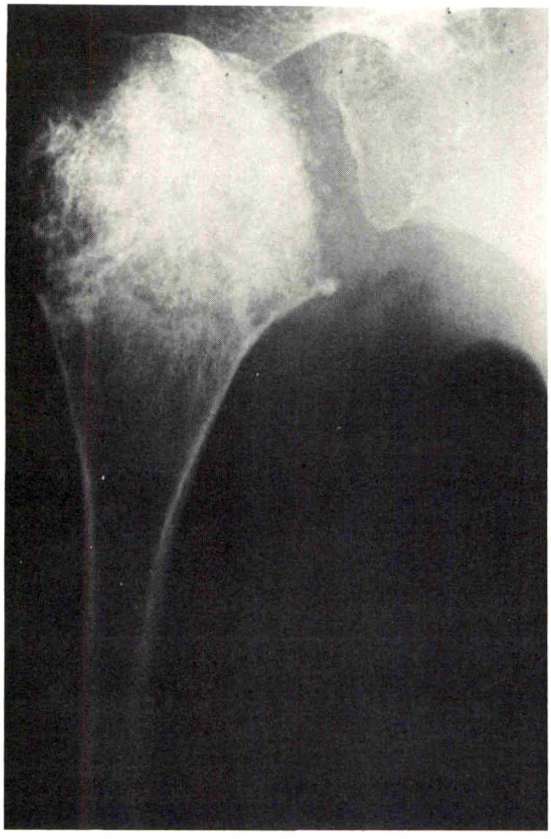


Fig. 10. The cloud-like epiphyseal and metaphyseal calcifications in a 12 year old's proximal humerus.

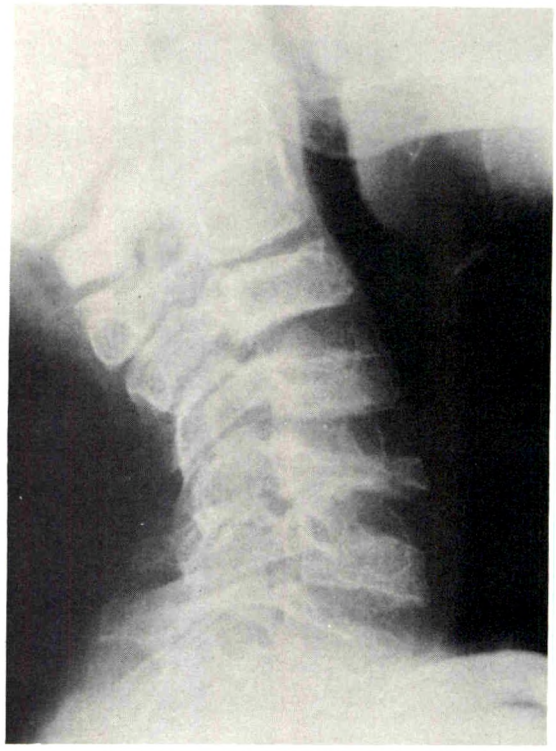


Fig. 11. A 7 year old's cervical spine showing the markedly enlarged C2 with an ununited odontoid. Platyspondyly is apparent.

Fig. 12. An ossification defect is apparent in this 4 year old's cervical vertebral body.

Fig. 9. (*A* and *B*) A 4 year old's knees revealing both the soft tissue and bone changes.

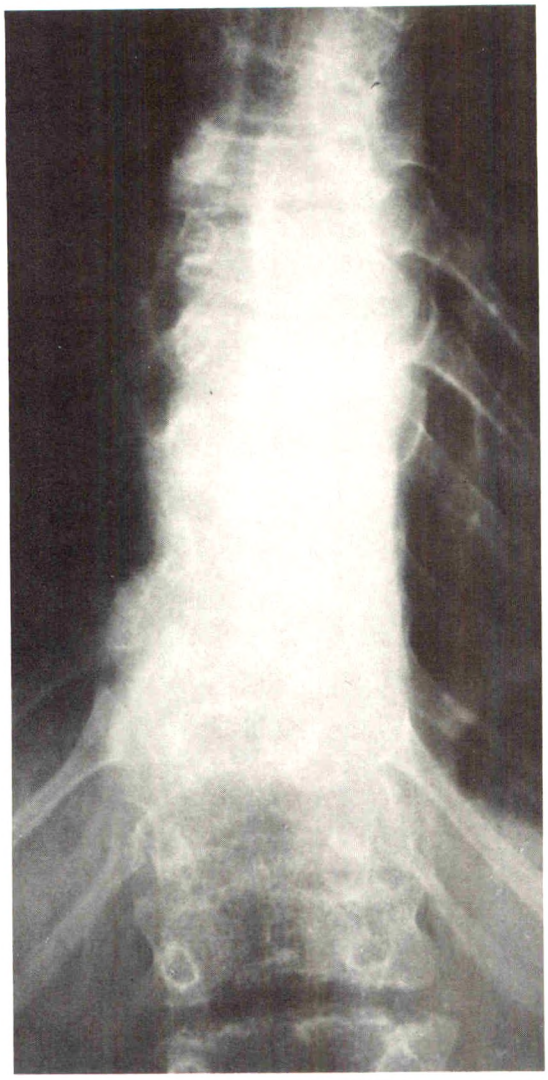


Fig. 13. A cloud effect involving the spine of a 12 year old.

ing pelvis as epiphyseal fusion has occurred. A hip arthrogram was performed in a patient at 12 years of age revealing a poorly formed anlage of capital femoral epiphysis with a smooth contour (Fig. 7; and 8).

THE KNEES

The 3 year old with Kniest syndrome already has characteristic changes at the knees. Diffuse osteoporosis is present. The femora are still somewhat club-shaped with metaphyseal flaring. The ossification centers at the knees are quite irregular. From about 3 years on, there is an increased density about the joint space with capsular swelling, and about 1 year later, peculiar cloud-like calcifications occur on both sides of the epiphyseal plate. The epiphyses are quite large and by 4 years of age cover the entire extent of the widened metaphyses. Some joint space narrowing is apparent (Fig. 9, *A* and *B*).

These characteristic changes are found throughout late childhood and adolescence. By 12 years of age, the large ends of the bones persist after epiphyseal fusion and still some remnants of the cloud calcifications occur; the latter disappearing by adulthood.

THE REMAINING LONG BONES

The arms as well as the legs show rhizo-

Fig. 14. A cloud effect involving the spine of a 12 year old.

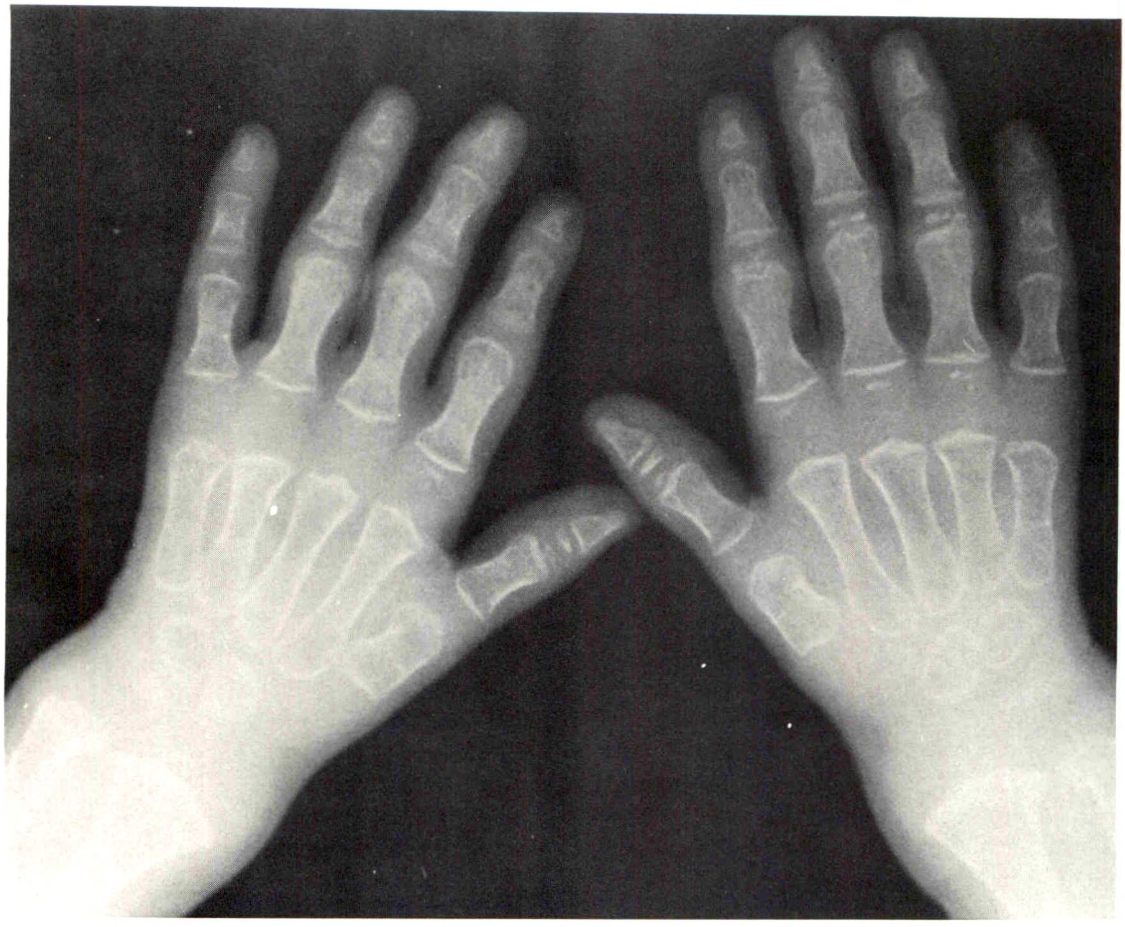


Fig. 15. A 5 year old's hands showing epiphyseal and carpal retardation, fragmented accessory centers, soft tissue swelling, and generalized osteopenia.

melic shortening; however, the amount of rhizomelia is variable. Metaphyseal and epiphyseal changes are similar to changes at the knees, but are rarely as severe except at the proximal humeral area (Fig. 10). There is a generalized osteopenia of all of the bones, but most marked at the ends of the long bones. After epiphyseal fusion, the cloud-like calcification of the epiphyses and metaphyses tends to disappear, the adult long bones appearing rhizomelic with clubbed ends.

THE SPINE

The newborn spine, as previously described, has platyspondyly and elongation of vertebral bodies. Vertical clefts are present which usually disappear during the first year. By 3 years of age, one has generalized vertebral flattening and elongation, often accentuated in the thoracic spine. A lumbar lordosis and kyphoscoliosis become apparent.

The cervical spine shows similar platyspondyly, but may have a markedly enlarged C_2 with an ununited odontoid (Fig. 11). Notch defects in this region may persist even after 4 years of age (Fig. 12). As in the long bones, the cloud effect appears in late childhood, involving the spine in a characteristic pattern (Fig. 13; and 14).

THE HANDS

The roentgenograms of the hands are quite distinctive in this syndrome. Under a year of age, the hands appear quite normal roentgenographically, but with the appearance of the epiphyseal centers of metacarpals and phalanges, changes become more apparent. Epiphyseal ossification is de-

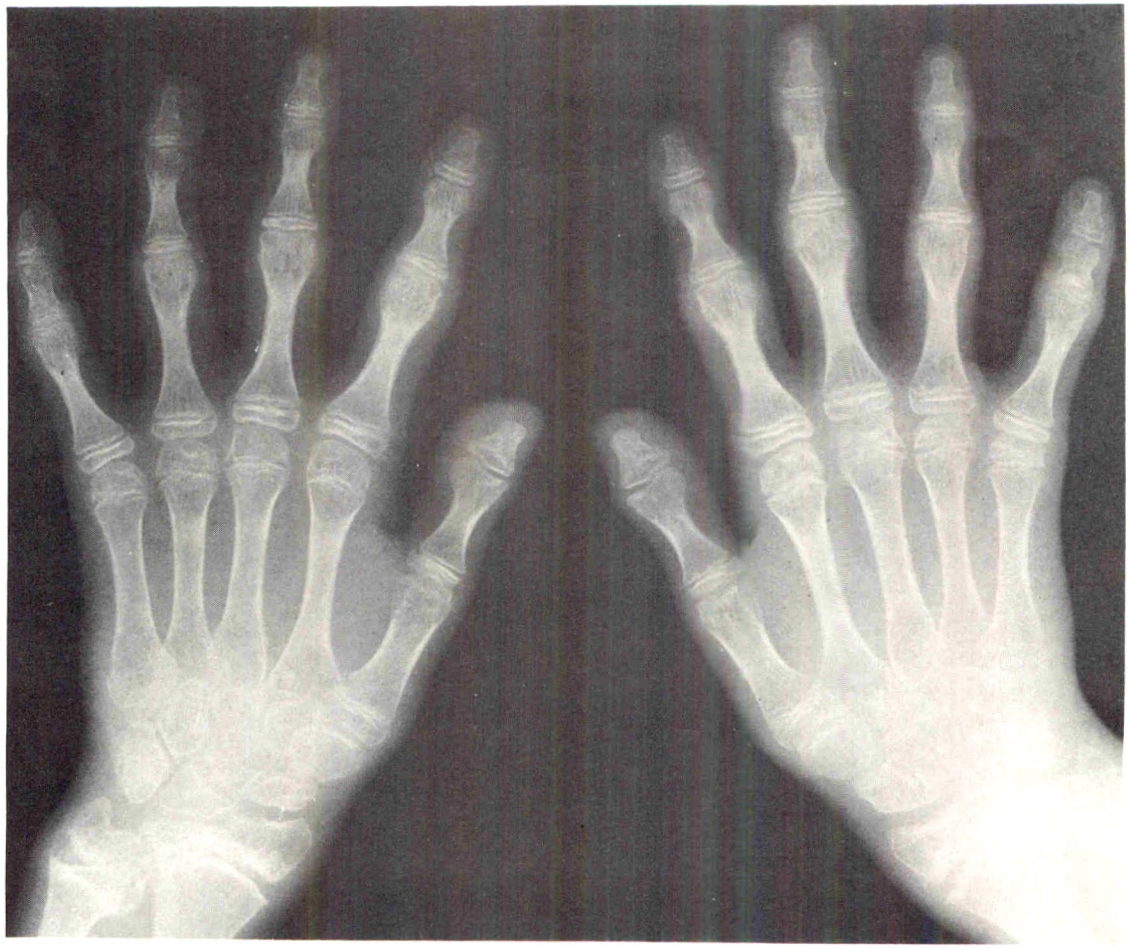


Fig. 16. A 12 year old's hands with characteristic changes of bones and soft tissues.

layed. A generalized osteoporosis is seen with slight widening of the medullary canal and minimal shortening.

There is soft tissue swelling and increased density at all the interphalangeal joints, but most marked at the proximal interphalangeal areas of all digits. Epiphyseal centers are faint, but normal in shape. In the proximal interphalangeal regions, there are fragmented accessory centers involving primarily the distal portions of many phalanges (Fig. 15). Early, the carpal centers are normally shaped, although osteoporotic, but after 3 years of age, the carpal centers take on unusual shapes and sizes.

After 6 years of age, the hands of all patients are alike. Narrowing of all joint spaces including the intercarpal area has occurred. Large, malformed carpal centers are present. The epiphyses of the hand, especially of the metacarpals, have become flattened on the side opposite the epiphyseal plate. The fragmented accessory centers have fused with and disappeared into the adjacent phalanges.

At 12 years of age, strikingly similar hands with bulbous enlargement of both ends of the bones and diffuse osteoporosis is apparent. The tuft of the thumb is frequently short (Fig. 16).

PATHOLOGY

The chondro-osseous histopathology in the Kniest syndrome is markedly abnormal and quite distinctive[4–7] (Fig. 17). Resting cartilage contains large chondrocytes which lie in a very loosely woven matrix, containing numerous empty spaces. Because of this holey appearance, the term "Swiss Cheese Cartilage syndrome" has been pro-

posed for this disorder.[4] The growth plate is composed of an extremely hypercellular cartilage containing large chondrocytes with little intervening matrix. This results in the formation of broad, short, irregular spicules of calcified cartilage and bone. Ultrastructural studies of this cartilage have revealed chondrocytes filled with dilated cisternae of endoplasmic reticulum.[7] The Swiss Cheese appearance of the resting cartilage in this disorder is quite characteristic and has not been observed in any of the other chondrodystrophies.[6,7]

GENETICS

The Kniest syndrome affects both males and females in approximately equal proportions. With the exception of one kindred reported by Maroteaux and Spranger,[3] all cases have been sporadic. This would suggest an autosomal dominant mode of inheritance, but further affected kindreds will have to be described to confirm this hypothesis.

DISCUSSION

The Kniest syndrome is a distinct chondrodystrophy associated with predominantly short trunked dwarfism with shortened limbs, flat facies, frequent cleft palate, hearing loss and myopia; there are characteristic cartilaginous histopathology and diagnostic skeletal roentgenograms. The characteristic roentgenographic findings in the Kniest syndrome include moderate platyspondyly with elongated vertebral bodies that manifest vertical clefts in early life and by late childhood, a cloud or smoke effect adjacent to vertebral epiphyses. This cloud effect is quite characteristic in other epimetaphyseal regions of the long bones as well. The hands are quite unusual in development, with widening at the ends of bones, fragmented accessory centers in the phalanges and epiphyseal flattening in the metacarpals. Dr. A. Poznanski has evaluated several of these cases of the Kniest syndrome and believes they all express a similar pattern profile (Fig. 18).

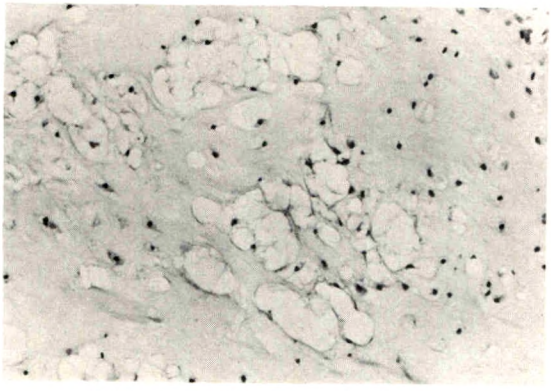


Fig. 17. "Swiss Cheese Cartilage."

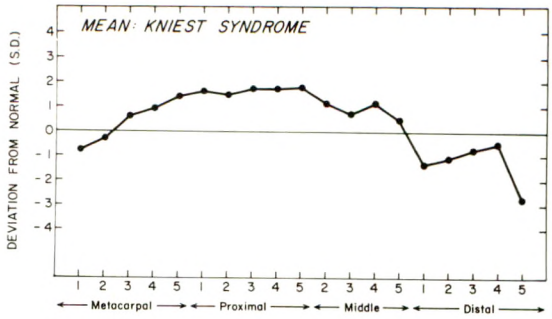


Fig. 18. Pattern profile of Kniest syndrome.

This syndrome has been confused with metatropic dwarfism[1,2] and has been referred to as metatropic dwarfism, Type II and pseudometatropic dwarfism.[8] This confusion arises because of the "dumbbell shaped" long bones found in both conditions. However, during the newborn period, the time of perhaps greatest confusion, the wafer vertebral bodies of metatropic dwarfism are quite different from the moderate elongated platyspondyly of the Kniest syndrome and do not contain the typical clefts described here. Also, the ribs in metatropic dwarfism are quite short, unlike the normal, slightly cupped ribs of a newborn with the Kniest syndrome. These features alone appear to be sufficient to separate these two conditions, even in early life.

Spondyloepiphyseal dysplasia congenita (SED congenita) is easily distinguished from the Kniest syndrome, since the full-term newborn with SED congenita has no ossification centers at the knees, more severe pubic as well as ischial hypoplasia and the femora do not have a dumbbell shape. Furthermore, vertical clefts of the

vertebrae are not part of SED congenita. Later in life, the characteristic cloud-like calcifications and hand findings in the Kniest syndrome distinguish it from SED congenita and the other spondyloepiphyseal dysplasias. Thus, the Kniest syndrome is a specific chondrodystrophy that has pathognomonic roentgenographic features.

SUMMARY

The Kniest syndrome is a newly defined chondrodystrophy consisting of disproportionate dwarfism with kyphoscoliosis, flat facies with prominent eyes, myopia, cleft palate, hearing loss and limited joint motion. As a result of a collaborative study of 12 patients, the roentgenographic features of this syndrome have been found to be diagnostic.

The major roentgenographic features consist of:

1. Flat, markedly elongated irregular vertebral bodies, which have superior-inferior defects in their midportion during infancy and early childhood.

2. Dumbbell shaped long bones which in later life show epiphyseal ossification delay and irregularity, as well as expanded metaphyses with a cloud-like effect on both sides of the epiphyseal plate.

3. Characteristic flattened and squared off epiphyses of the hands with joint space narrowing.

Biopsies of costochondral junction and iliac crest reveal identical histologic and ultrastructural abnormalities which differ from all other chondrodystrophies. Throughout the cartilage are large hypertrophic cells whose surrounding matrix is loose and irregular in staining ability with large holes resembling Swiss cheese.

The Kniest syndrome represents a distinct chondrodystrophy diagnosable roentgenographically and associated with specific abnormalities in cartilage structure.

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We wish to thank Dr. A. Poznanski for the pattern profile performed on some of our patients and Figure 18.

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Vol. 123, No. 4

VASCULAR TUMORS OF THE SALIVARY GLANDS IN CHILDREN*

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SALIVARY gland tumors are uncommon in children. However, in all reported series vascular tumors are the most frequent, especially the hemangioma. As a general rule the tumors of the salivary glands are most commonly encountered in the parotid, whereas lithiasis is more common in the submaxillary gland. As regards tumors the same rule applies in children: they are much more common in the parotid.

We wish to report 4 cases of vascular tumors of the salivary glands and to discuss the clinical and pathologic presentation of these tumors, stressing especially some rather typical roentgenographic findings.

REPORT OF CASES

CASE I. M.C., a 15 year old female, had noted a mass in her left parotid region $4\frac{1}{2}$ years before her admission to the hospital. She was otherwise asymptomatic. The physical examination was negative except for a soft, 4×5 cm. tumor in the left parotid. A plain film roentgenogram of the neck showed nodular calcifications (Fig. 1) and a sialogram disclosed a 5 cm. mass harboring rare calcifications (Fig. 2, *A* and *B*). A left carotid arteriogram showed the poor vascularization of the tumor (Fig. 3).

The tumor was surgically excised and it appeared macroscopically as a soft mass, dark in color and showing numerous holes or cells. At microscopy, the diagnosis of cavernous angioma was confirmed.

CASE II. C.C., a 3 month old female, was admitted for a tumor of the left parotid gland. The mass was remittent, mobile and painless. The roentgenograms revealed the presence of a soft tissue mass displacing the external ear (Fig. 4).

The mass was first thought to be a branchial cyst but 1 month later it had enlarged and it was decided to proceed to a parotidectomy. At pathology, the tumor proved to be hemangioendothelioma of the parotid.

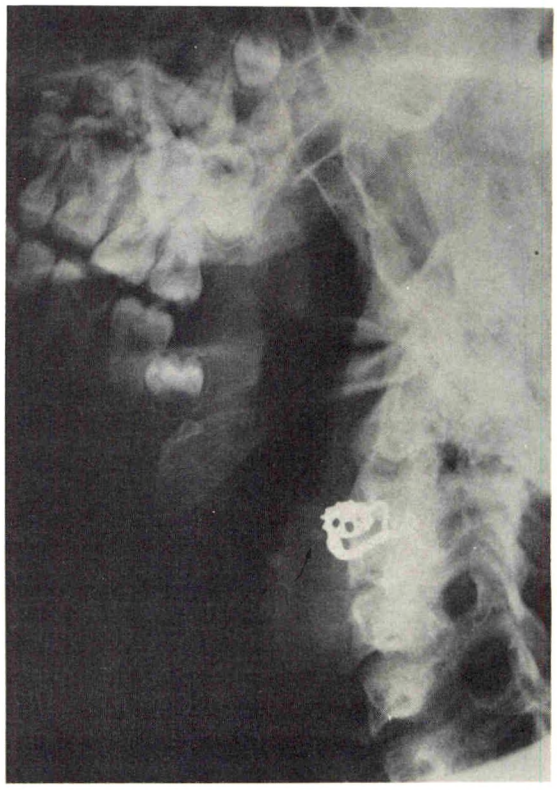

FIG. 1. Case I. Two round calcifications (arrows), rather typical of phleboliths, are well seen.

CASE III. D.H., a white female, was 6 years old when a cavernous angioma of the mixed type (*i.e.*, venous and lymphatic) was discovered along the right anterior jugular vein. The medical record revealed that a small tumor appearing on exertion had been present for at least 3 years in this region.

At 13 years of age she had a mass in the *left* submaxillary region. Plain film roentgenograms showed calcifications (Fig. 5) in the submaxillary gland and an attempt at sialography was unsuccessful because of interstitial extravasation of the opaque medium.

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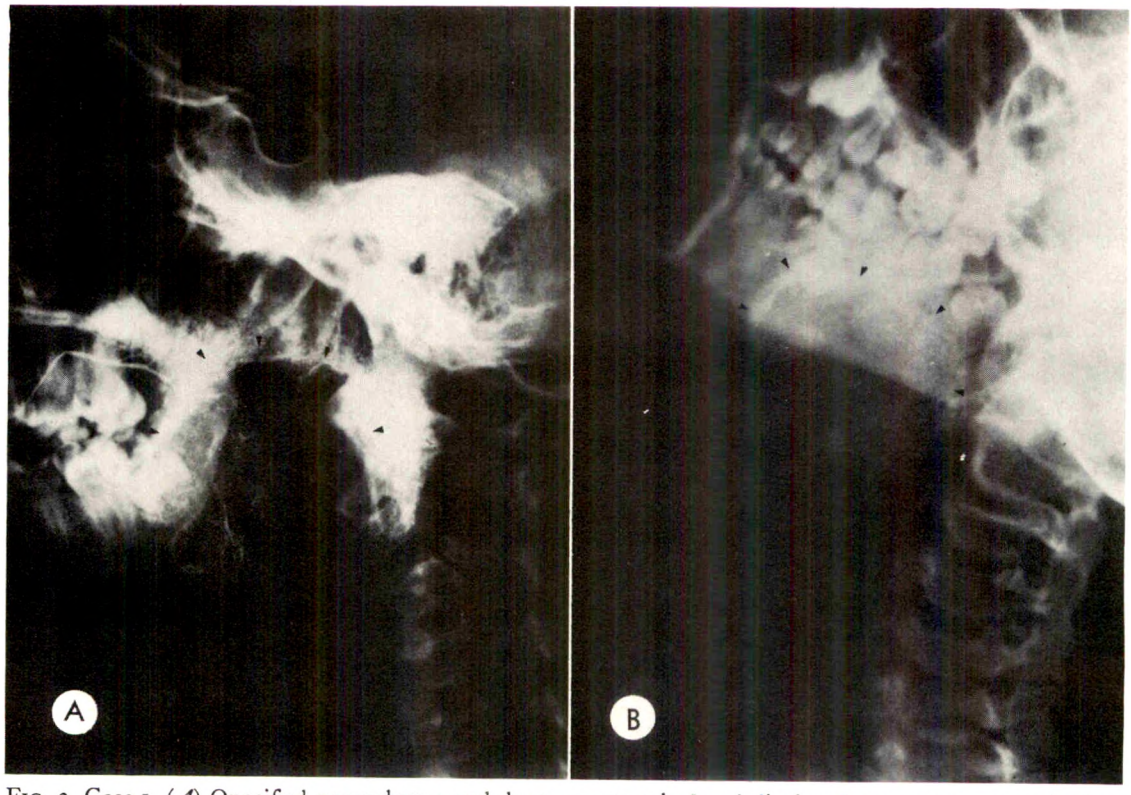

Fig. 2. Case I. (*A*) Opacified parenchyma and ducts are stretched and displaced over a 5 cm. mass harboring the calcifications seen on plain roentgenogram. (*B*) Later phase of sialography. Note again the large central filling defect produced by the mass.

The gland was surgically excised and the tumor proved to be a cavernous capillary hemangioma.

Case IV. A 1 month old male was brought to the hospital because of crisis of cyanosis and tachypnea. A left cervical tumor had been noted at birth. The physical examination revealed a soft mass over which the skin appeared slightly blue. The mass was excised surgically and at microscopy proved to be a cavernous lymphangioma.

Seven months later, the mass had recurred and now invaded the whole cheek and extended to the mandibular region. The infant had been seen at irregular intervals but unfortunately no radiography was obtained. When the child was 9 years old, plain film roentgenograms of the neck (Fig. 6) showed calcifications within the mass and sialography (Fig. 7) was performed which revealed a non-homogeneous opacification with absence of opaque medium in the region where the calcifications were seen.

DISCUSSION

Hemangioma of the salivary gland, although uncommon, is the most common salivary tumor in infants and children. It has a striking female predilection. Usually a mass is noted, most commonly in the parotid region, within the first 6 months of life. The mass usually enlarges rapidly. Less frequently, the tumor may not be manifested until childhood.

The lymphangioma is also a vascular tumor that may affect the salivary glands, but it is rarely limited to these glands. Usually the surrounding tissues are also involved.

Radiology may be very useful in arriving at a preoperative diagnosis. A plain film roentgenogram of the neck will show a soft

tissue mass (Fig. 4) within which calcifications (Fig. 1–6) are commonly seen such as occurred in 3 of our 4 cases. Sialography (Fig. 2, *A* and *B*; and 7) reveals the presence of a space occupying lesion displacing and stretching the neighboring ducts. This is not specific for vascular tumors however, and sialography may not be necessary if calcifications, especially phleboliths, are seen on the plain film roentgenogram. We believe that the association of a salivary gland mass harboring calcifications and occurring in an infant, or a young child especially if she is a female, is almost diagnostic of hemangioma.

However, as stated by Martinez-Mora *et al.*,[7] sialography by showing the extension of the tumor and the involvement or absence of involvement of the glandular parenchyma helps to plan the surgical ap-

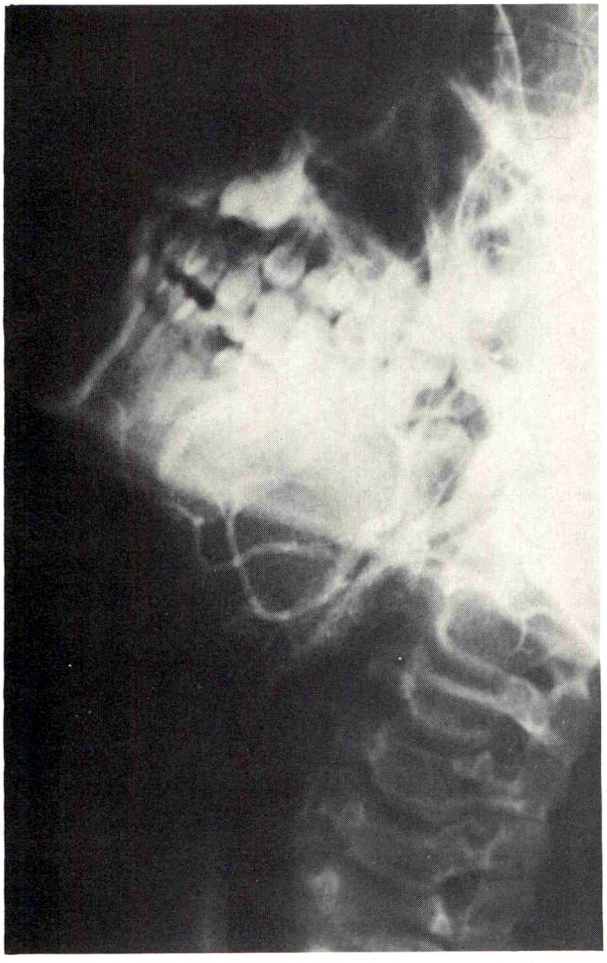

Fig. 3. Case 1. Carotid arteriogram showing the poor vascularization of the tumor.

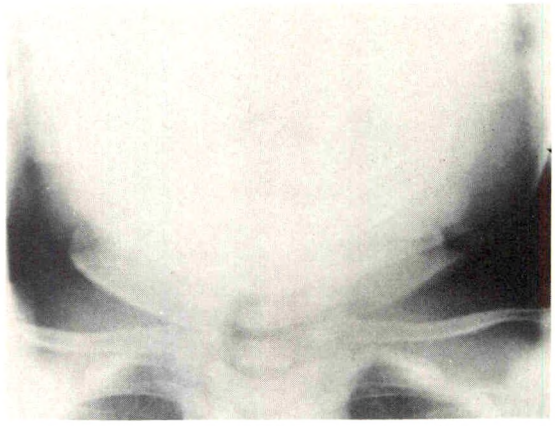

Fig. 4. Case II. Soft tissue mass (arrow) displacing the external ear.

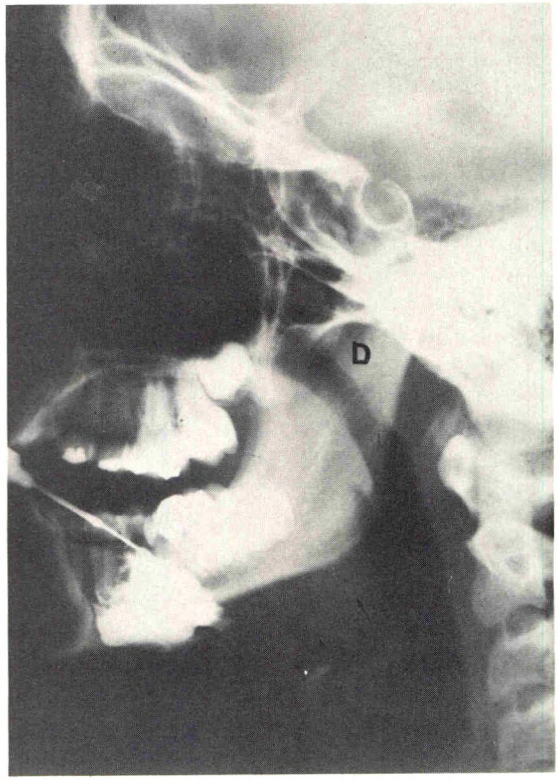

Fig. 5. Case III. Three round calcifications (arrows) are seen in the region of the submaxillary gland. Note the extravasated opaque medium from an unsuccessful attempt at sialography.

Fig. 6. Case IV. Plain film roentgenogram showing a round calcification.

proach and the extent of the excision.

An arteriogram (Fig. 3) was obtained in only 1 case and it showed an "avascular" expanding lesion. The macroscopic aspect of these tumors is congestive, purple red. Microscopically, in hemangiomas, the lobules are replaced by vascular formations mostly of the capillary size. In lymphangiomas, the lobules are not replaced, but they are displaced and separated by "lymph-containing caverns."[1]

The treatment of choice was formerly surgical excision, but according to Williams,[9] these tumors will generally disappear spontaneously around the age of 5 years. Surgery, therefore, should be reserved for those cases which do not regress or for those cases making their appearance late in childhood. On the other hand, malignant tumors require a more aggressive treatment, and excluding the hemangioma and lymphangioma, tumors of the salivary glands in children are more commonly malignant than benign. Therefore, it is important to arrive at a precise diagnosis and plain roentgenograms plus sialography may prove to be most helpful.

SUMMARY

Salivary gland tumors, although uncommon in children, are mostly vascular tumors. The latter may have a rather characteristic roentgenographic appearance which allows a fairly precise preoperative diagnosis.

Since descriptions of these tumors in the radiologic literature are very scarce, we wish to present 4 such cases.

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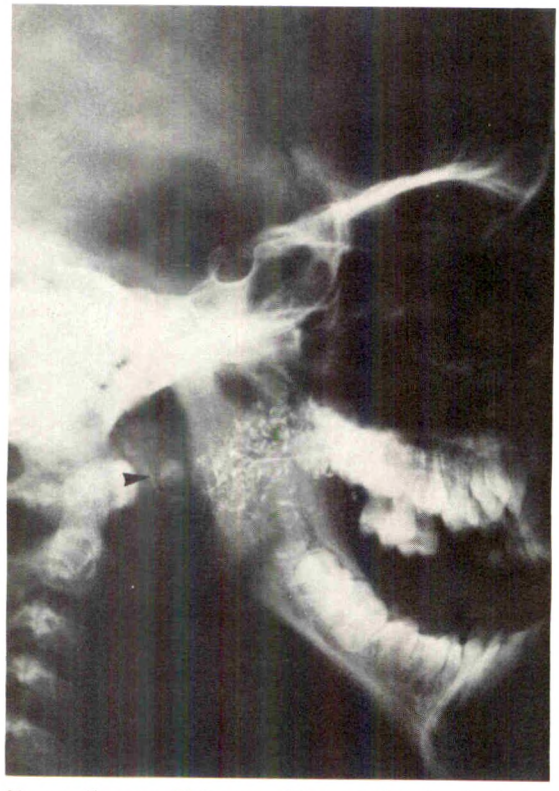

Fig. 7. Case IV. Sialogram. The calcification is shown to be within an expanding lesion of the parotid (arrowhead).

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ROENTGENOLOGIC ASPECTS OF ADULT CRETINISM*

TWO CASE REPORTS AND REVIEW OF THE LITERATURE

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WHILE it is of infinitely more importance to diagnose congenital hypothyroidism in early infancy, it is of more than passing interest to identify, even in later years, the adult sporadic cretin or the adult hypothyroid endemic cretin. Relief or decrease in some of the symptoms associated with these forms of cretinism can be achieved with adequate thyroid replacement therapy despite a chronic history. Therefore, identification of these adult cretins can, and should, be more than an academic satisfaction. A distinction is made in reference to the type of cretin, because it has been shown that hypothyroidism is a constant feature of only the sporadic cretin and the myxedematous endemic cretin is euthyroid.[7,12,13]

Congenital hypothyroidism is the most common childhood endocrine abnormality. Its recognition dates before Paracelsus.[6] Descriptions of goiterous, dwarfed, and mentally retarded adults can be found in early writings of many cultures, and, while the epidemiology and etiology have been known for over 100 years, countless generations of iodine deficient populations have existed. In fact, deep within primitive civilizations, endemic goiter persists and many of these are of the hypothyroid type. Kelly and Snedden[15] estimated that there were perhaps 200 million goiterous people in the world in 1958. Their review of 114 countries revealed worldwide endemic areas with the incidence being somewhat inversely proportional to geographic isolation and remoteness. In 1929, although Olson[23] was able to locate endemic regions within the northwest and Great Lakes states, increased mobility over the past half century has all but eradicated this disease in such areas of the United States. It is with difficulty that cases of untreated, adult sporadic cretins or adult hypothyroid endemic cretins can be found within this country. Fortunately, the early recognition of congenital or infantile hypothyroidism has greatly decreased the chance of the isolated case to go untreated for any length of time.

In this paper the authors review the literature and emphasize the roentgenologic aspects of 2 cases of adult sporadic cretins seen at Strong Memorial Hospital (SMH), neither of whom had been on thyroid replacement therapy prior to their presentations and metabolic evaluations.

REPORT OF CASES

CASE 1. E.G. (SMH No. 73–96–82) was a 29 year old Mexican-American male born in Texas who allegedly had ceased to grow sometime between 8 and 11 years of age. Although he completed the eighth grade, his intelligence was below normal. He had no knowledge of having thyroid disease and his prior medical history lacked significant illnesses. His first loss of a deciduous tooth was at age 26 years and that was by surgical extraction because of extensive carious disease. There was no family history of thyroid disease.

Physically, he was a short (124.8 cm.), stocky (30.6 kg.) man with a protuberant abdomen. His fingernails were soft, his skin dry, and his speech thick. He lacked pubic hair and had enlarged testicles.[18]

Laboratory Findings. Radioactive iodine uptake (RAIU) at 2, 6, and 24 hours was 2 per cent; thyroid stimulating hormone (TSH) was greater than 80 micrograms (μg.) per cent; 17-ketosteroid level was 4.5 milligrams (mg.)/24 hours; thyroxine (T_4, Murphy-Patee) was 1.2 μg. per cent.

His roentgenographic manifestations are listed in Table 1 and selectively demonstrated in Figures 1, 2, and 3.

Treatment. Fifty μg. of Synthroid daily

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Table I

ROENTGENOLOGIC FINDINGS IN ADULT CRETINISM: 2 ROCHESTER CASES

	Case I	Case II
Skull	Short basiocciput Narrow diploic space Enlarged sella turcica Petro-mastoid hypoplasia	Short basiocciput Narrow diploic space Enlarged sella turcica Petro-mastoid hypoplasia
Facial Bones	Hypoplastic paranasal sinuses Unerupted permanent teeth Prognathism Hypoplastic nasal bones	Hypoplastic paranasal sinuses Unerupted permanent teeth Prognathism with widened mandibular angle Hypoplastic nasal bones
Vertebral Column	Kyphosis Persistent canals of Hahn "Bullet" shaped vertebrae (all) "Wide" disk spaces Pseudosubluxation of C1 on C2 Unfused odontoid and vertebral apophyses	Kyphosis Persistent canals of Hahn "Bullet" shaped vertebrae (all) "Wide" disk spaces Unfused ring apophyses
Pelvis		Unfused iliac apophyses Hypoplastic ilia
Limbs	Coxa vara, magna, and plana Short metacarpals and metatarsals Delayed ossification of sternum "Epiphyseal dysgenesis" of humeral, femoral, tibial epiphyses and patellae Post-growth arrest lines	Coxa vara, magna, and plana Short metacarpals and metatarsals Delayed carpal ossification "Epiphyseal dysgenesis" of humeral and femoral epiphyses, and patellae
Miscellaneous (Extra Skeletal)	Premature arterial calcification Nephrocalcinosis Enlarged testicles	Premature arterial calcification Nephrocalcinosis Dystrophic calcification within parotid gland

rapidly improved his speed of physical movement, speech and "mental function." His bone age advanced from 6 years to 14.5 years following a 12 month period of therapy.

Comment. Clinical, laboratory and roentgenologic findings established a diagnosis of adult sporadic cretinism. Despite the alleged mid-childhood recognition of retarded growth, the roentgenologic finding of epiphyseal dysgenesis in the femoral and tibial epiphyses establishes congenital onset of the hypothyroid state.

Case II. J.M. (SMH No. 67–51–74), a 41 year old mentally retarded man, had been seen medically for rectal prolapse secondary to chronic constipation. Hematuria was also present and evaluation of this was undertaken as well. Following this evaluation, a work-up for his short stature and mental retardation was commenced.

He allegedly had been on thyroid therapy as an infant; however, if he had been on thyroid replacement, the duration of therapy was limited. The roentgenologic evaluation supported this hypothesis. His family history revealed that his mother had a goiter but apparently she was not hypothyroid.

On physical examination, he was a short man (height: 140 cm.) who appeared immature. Skin was thin and transparent, body hair was absent, abdomen protuberant (Fig. 4), and his thyroid gland was not palpable.

Laboratory Findings. Protein bound iodine (PBI) was 1.0 μg. per cent; 17-ketosteroid level

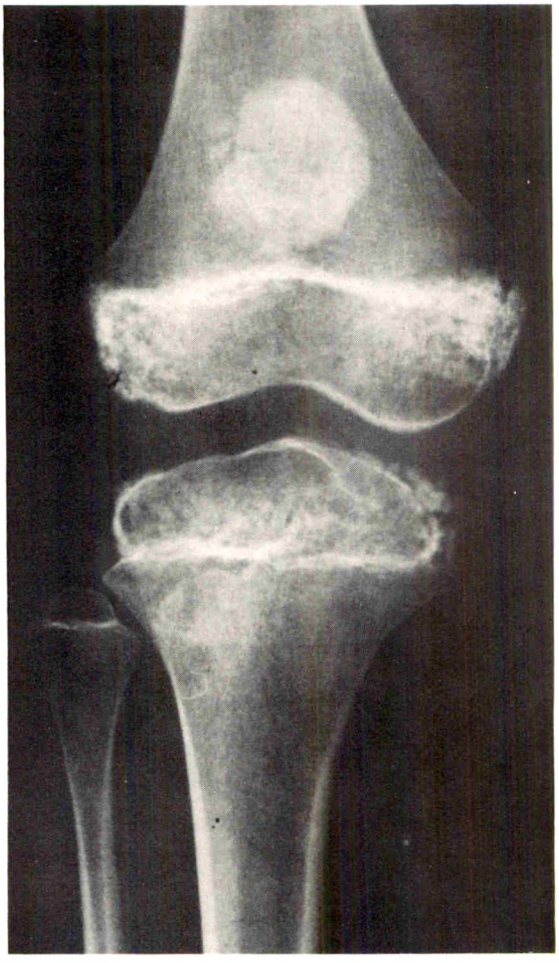

Fig. 1. Case 1. Anteroposterior roentgenogram of right knee: "epiphyseal dysgenesis" of distal femoral and proximal tibial epiphyses and patella; delayed fusion of epiphyses.

was 4.0 mg./24 hours; T_4 (Murphy-Patee) was 5.7 μg. per cent; and triiodothyronine (T_3) was 9.1 per cent.

His roentgenologic manifestations are listed in Table 1 and demonstrated in Figures 5, *A* and *B*; 6, *A–C*; 7; and 8.

Treatment. He was treated with 25 μg. of Synthroid daily with resultant dramatic decrease in lethargy, somnolence and constipation.

Comment. The clinical, laboratory and roentgenologic findings established the diagnosis of adult sporadic cretinism. The mother, although having a goiter, was not hypothyroid and the other family members were free of the condition.

DISCUSSION

Extrapolation from childhood to adult roentgenographic manifestations of untreated sporadic cretins is not difficult, for the common denominator is disordered ossification and associated delayed skeletal maturation. Ubiquitously displayed, this delayed maturation accounts for most of the roentgenographic findings associated with this now rare disease.[20,26]

Portions of the skull that arise from enchondral ossification, such as the basiocciput and sphenoid bones, are represented roentgenographically by shortening in the former, and underdevelopment and delayed aeration in the latter.[5]

Sutures may remain unfused and intersutural bones are common. Hypoplastic nasal bones, hypoplastic mastoids and unfused mandibular symphyses are also seen.

In both of our patients a relative progna-

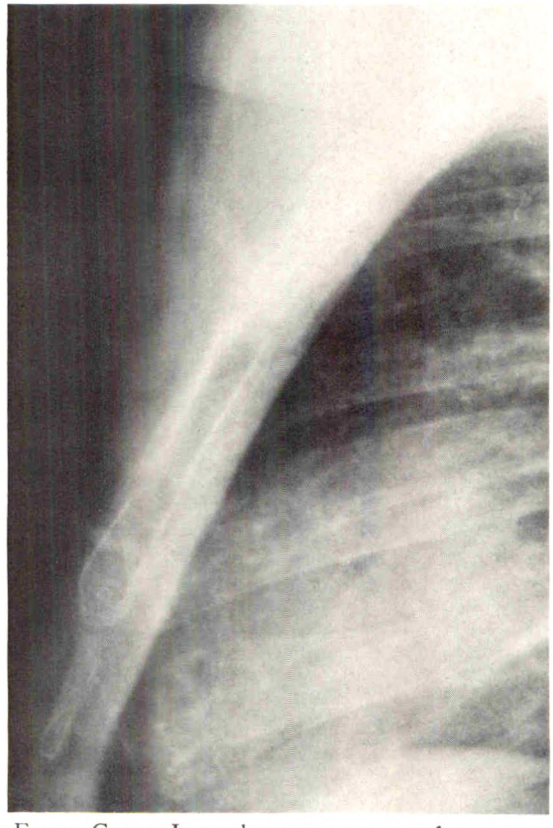

Fig. 2. Case 1. Lateral roentgenogram of sternum: persistent segmentation of sternum.

thism was present with distortion and anterior protrusion of the maxillary front teeth. This has been thought to be secondary to overgrowth of the maxillary incisors. Also contributing to this shortened maxilla is the absence or hypoplasia of the paranasal sinuses.[8] The combination of maxillary hypoplasia and shortened base contributes to the flat facies of these patients. The mandible is often hypoplastic with an increased mandibular angle.[2]

In 1851 Niepce[22] described the abnormally large sella turcica found in most adult cretins. He described sella turcicas 3 to 4 times normal size. Subsequently, it has been shown that the anteroposterior and depth dimensions of the sella turcica are increased relative to the patient's height.[14] This disproportionate size of the sella turcica is probably not a manifestation of abnormal skeletal development, but is secondary to pituitary hyperplasia resulting from increased TSH elaboration. Both of our patients exhibited these findings (Fig. 5, *A* and *B*).

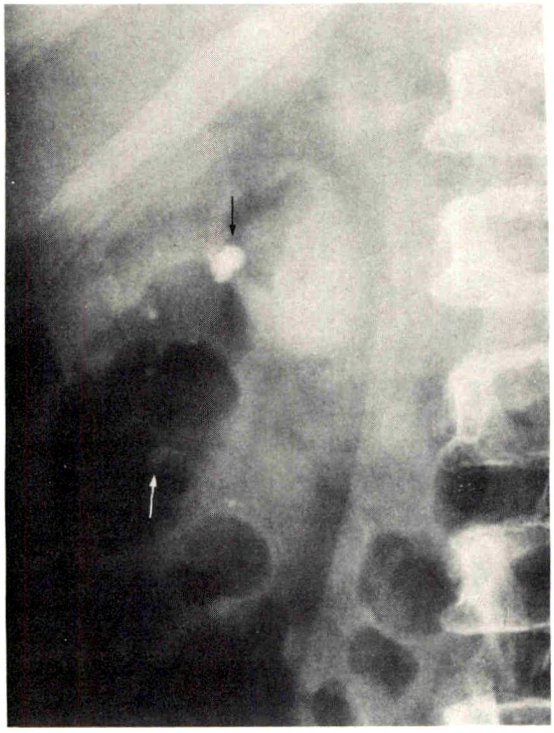

Fig. 3. Case 1. Anteroposterior roentgenogram of right renal area: nephrocalcinosis (arrows).

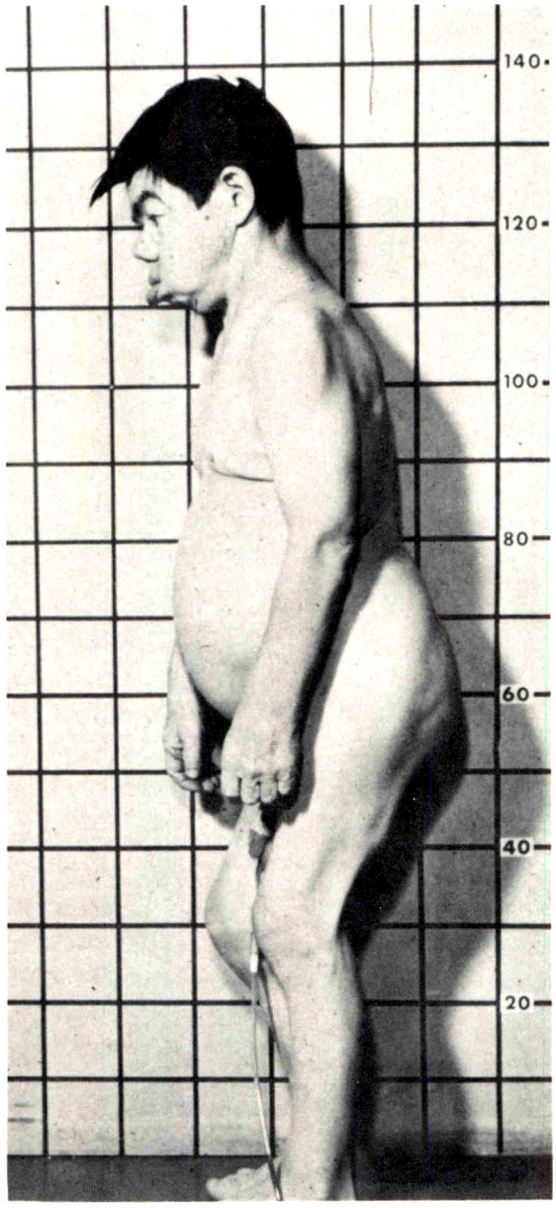

Fig. 4. Case 11. Lateral photograph. Note physical findings as described in text.

The vertebrae show many interesting findings.[1,9] In the child and adolescent cretin, classically the 12th thoracic and 1st lumbar vertebral bodies are short and "bullet shaped." In our 2 patients all the vertebral bodies were shortened (Fig. 6, *A–C*). It is of interest that the 12th thoracic and 1st lumbar vertebral bodies are the most frequently traumatized in the general population. Perhaps inordinate

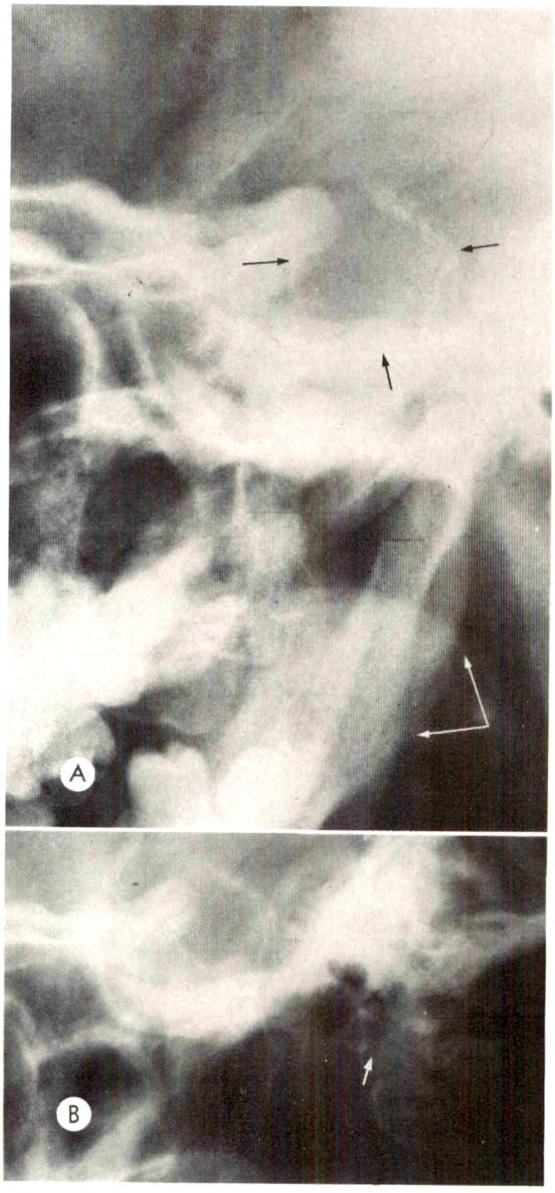

FIG. 5. Case 11. (*A*) Lateral, coned view of mandible and sella turcica: enlarged, "half-moon" sella turcica (black arrows); widened mandibular angle (white arrows). (*B*) Lateral, coned view of sella turcica and superior cervical spine: deep, "half moon" sella turcica; pseudosubluxation of odontoid process relative to anterior body of atlas (white arrow).

stress at the thoracolumbar area combined with a decreased nerve conduction[21] and/or a relative insensitivity to pain, result in the vertebral body abnormalities. Poorly ossified and unfused ring apophyses and persistent nutrient canals of Hahn (as may be seen in the adolescent cretin) were also noted in our patients. In the 2 reported cases, the intervertebral disk spaces are relatively widened, a finding not previously described (Fig. 6, *A–C*).

Both of the described cases showed a greater than normal distance for the patients' ages between the anterior margin of the odontoid and the posterior margin of the anterior arch of the 1st cervical vertebra (Fig. 5*B*; and 6*A*). This represents persistence of a juvenile characteristic, "pseudosubluxation," another finding not previously described.

Manifestations of this disease are also apparent in the appendicular skeleton. "Cretinoid epiphyseal dysgenesis," a descriptive term with mechanistic implications, was first used by Reilly and Smyth in 1937,[24] although the finding was described earlier by others.[17,19] It represents a manifestation of disordered ossification and delayed maturation and is characterized by a generalized irregular mosaic pattern. The delayed ossification results in growth of individual cartilage cells with delayed multicentric ossification at the epiphyses, as opposed to the usual unifocal, central ossification. All but 2 of the 22 children reported by Wilkins and Fleischman[28] who had roentgenographic examinations had characteristic abnormalities, and this carries over into adulthood unless therapy intervenes. Wilkins and Fleischman further pointed out that only those epiphyseal centers which would normally undergo ossification at the time of the hypothyroid state will show typical dysgenesis. Most commonly this occurs with the humeral and femoral epiphyses (Fig. 1; and 7). Our patients had involvement of these 2 sites and, additionally, the patella (Fig. 1) and tarsus navicular. Secondary findings of coxa plana, magna and vara were also present. Postgrowth arrest lines were present in 1 of our patients (Case 1). This same patient also had persistent segmentation of the sternum (Fig. 2).

Unfused apophyses throughout the body

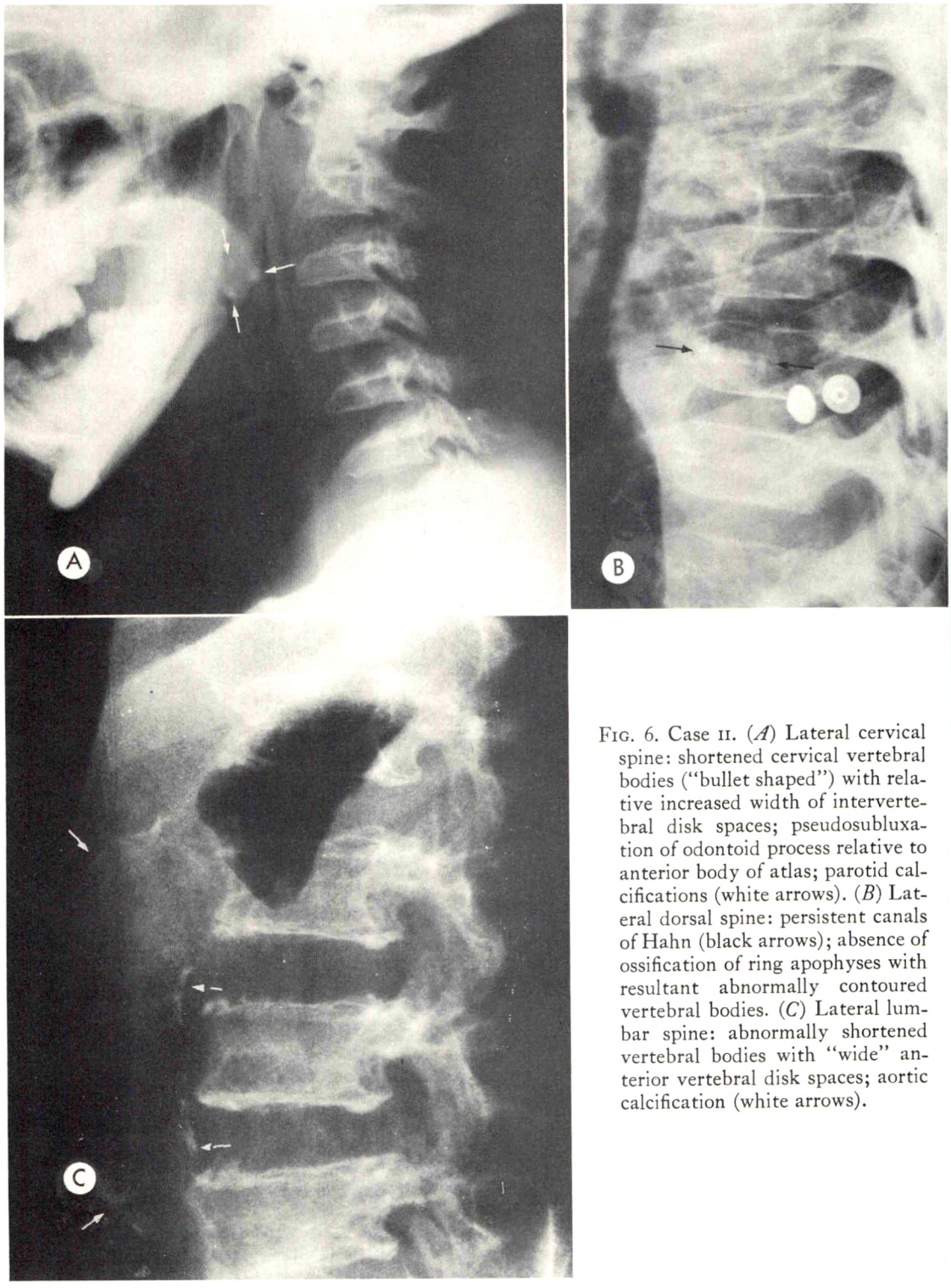

Fig. 6. Case II. (*A*) Lateral cervical spine: shortened cervical vertebral bodies ("bullet shaped") with relative increased width of intervertebral disk spaces; pseudosubluxation of odontoid process relative to anterior body of atlas; parotid calcifications (white arrows). (*B*) Lateral dorsal spine: persistent canals of Hahn (black arrows); absence of ossification of ring apophyses with resultant abnormally contoured vertebral bodies. (*C*) Lateral lumbar spine: abnormally shortened vertebral bodies with "wide" anterior vertebral disk spaces; aortic calcification (white arrows).

Fig. 7. Case II. Anteroposterior roentgenogram of right pelvis and hip: "epiphyseal dysgenesis" of right capital femoral epiphyses; unfused and poorly ossified iliac apophysis (black arrows).

are also frequently found, an example of which is the unfused iliac apophyses in Case II (Fig. 7).

Thyroid hormone exerts an influence upon the linear growth of long bones while it plays no role in the formation of periosteal bone. This is best exemplified by wide short metacarpals and metatarsals (Fig. 8).

Taken individually, each of the roentgenographic manifestations discussed can be found associated with a number of unrelated conditions or syndromes. However, the entire constellation of described findings is specific for the sporadic adult cretin.

Abnormal calcium metabolism and excretion is known to occur in the hypothyroid state.[3,25] Thyroxin apparently influences the renal threshold for calcium excretion. In the hypothyroid state this threshold is elevated with subsequent retention of calcium which is then deposited in bone. Although decreased bone mineralization has been described in hypothyroidism, Bateson and Chandler[4] described in all but one of their 11 cases a bony sclerosis in association with nephrocalcinosis. When the bony sclerosis occurs only in the periorbital region, this has been termed the "lunette" sign.

Hypersensitivity to vitamin D[10,11] sec-

Fig. 8. Case II. Posteroanterior roentgenogram of right hand; characteristic broad, squat metacarpals with incomplete epiphyseal fusion in wrist and phalanges.

ondary to delayed sterol breakdown results in overabsorption of calcium from the gastrointestinal tract with subsequent hypercalcemia, nephrocalcinosis[27] and, perhaps, dystrophic calcium deposits. Our 2 patients had nephrocalcinosis (Fig. 3) and Case II had calcium deposits in the parotid gland (Fig. 6*A*). The early arteriosclerotic changes[16] described in adult cretins is explainable on the same basis. With delayed sterol breakdown, hypercholesterolemia and an increased vascular deposition ensue. Case II had advanced arteriosclerotic changes for his age (Fig. 6*C*).

SUMMARY

Two cases of untreated adult sporadic cretins are presented with emphasis upon their roentgenographic findings. Explanations relative to these roentgenographic manifestations are presented, some proven and others hypothesized. A review of the major literature on the subject is also presented.

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PELVIC PNEUMOGRAPHY IN CHILDREN*

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ELUCIDATION of the nature of endocrine and gynecologic disorders in children and adolescents may be difficult when the diagnosis requires a knowledge of the size and nature of the internal pelvic structures. Pelvic examination may be unrewarding and often exploratory laparotomy is resorted to for the purpose of diagnosis. Pelvic pneumography has been extensively used in adults for the diagnosis of gynecologic disorders.[2,4,12] In children Kunstadter *et al.*[5] reported the use of this procedure first in 1953 and again in 1964,[6] and McDonough *et al.*[8,9] described its use in several pediatric cases.

We reported our initial experience with this procedure in 15 pediatric patients in 1971.[7] Subsequently, we have continued to use this technique with gratifying results and are now presenting a more extensive experience with 46 children and adolescents, over a 4 year period (April, 1969 to June, 1973).

MATERIAL AND METHOD

PATIENT GROUP

Pelvic pneumograms were obtained, where clinically indicated, as part of the diagnostic evaluation of patients referred to the UCLA Pediatric Endocrine Division. Informed consent was obtained for the procedure. The clinical information and findings are summarized in Table 1.

TECHNIQUE

Infants and most children under 10 years of age are examined under general anesthesia requiring a 24 hour period of hospitalization. In these cases endotracheal intubation is recommended to permit controlled ventilation because the Trendelenburg position and the presence of intraperitoneal gas may cause decreased pulmonary reserve. While the patient is anesthetized, pelvic examination can be performed if necessary. The bladder is emptied after the preliminary scout roentgenograms because any degree of bladder filling with urine may obscure visualization of pelvic structures. Catheterization with immediate removal of the catheter may be necessary in the anesthetized patient.

In older children and adolescents, the procedure is performed on an outpatient basis, under local anesthesia. One hour in the supine position, after completion of the study, is usually sufficient to allow enough gas resorption to minimize discomfort. Infants are prepared for the study with cleansing enemas, and older patients are given oral cathartics and enema.

A scout roentgenogram of the abdomen and pelvis is taken using standard roentgenographic technique to look for calcifications, abdominal masses, etc. This is followed by a second scout roentgenogram in the prone position and the roentgenographic exposure is adjusted so that the pelvic bones are barely visible. Films should be grossly "under exposed" in order to obtain maximum soft tissue-gas contrast.

Following scout roentgenograms, the patient is placed back in the supine position. The left upper quadrant is surgically cleansed and draped. An area approximately 3 finger breadths below the left costal margin and just lateral to the rectus muscle is chosen for placement of the needle. The skin and subcutaneous tissue, down to but not including the peritoneum, is infiltrated with local anesthetic. In the rare patient with splenomegaly, this point of entry should be avoided, and the needle

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TABLE I

SUMMARY OF CLINICAL AND ROENTGENOGRAPHIC FINDINGS*

Group	Classification	Age Range	No. of Patients Studied	Significant Clinical and Laboratory Findings	Pertinent Roentgenographic Findings
I.	Precocious puberty	7 mo.–8 yr.	11	Signs of isosexual precocity	1 ovarian granulosa cell tumor—7 studies with enlarged ovaries and uterus consistent with puberty
II.	Gonadal dysgenesis	13 yr.–20 yr.	4	Sex chromosome abnormalities	1 gonadoblastoma, 3 cases with gonadal streaks
III.	Primary amenorrhea	14 yr.–18 yr.	4	Normal female chromosomes	2 cases of congenital absence of the uterus
IV.	Secondary amenorrhea	14 yr.–17 yr.	3	Low gonadotropins	1 case of small ovaries and uterus consistent with hypogonadotropic state; 1 case of polycystic ovaries
V.	Hirsutism or virilization	12 yr.–20 yr.	10	Clitoromegaly, increased urine 17 ketosteroids	2 cases of adrenal adenoma found on scout roentgenograms or intravenous pyelograms, 5 cases of polycystic ovaries
VI.	Pseudohermaphroditism	6 wk.–16 yr.	9	Ambiguous genitalia, gynecomastia, chromosome abnormalities	establishment of internal anatomy
VII.	Previously uncertain diagnoses	12 yr.–16 yr.	5	Noncontributory	clarification of internal anatomy

* Details on all patients studied are available upon request to the authors.

may be inserted between the symphysis pubis and the umbilicus. A 2 or 3 inch, 18 gauge spinal needle is introduced perpendicular to the skin surface. The stylet is removed after penetrating the peritoneum and needle placement checked by introducing and then attempting to aspirate 3–5 cc. of air. If the air is easily recovered, the needle is probably in a subcutaneous pocket. When the tip is in the peritoneal cavity, the air cannot be easily reaspirated. The intraperitoneal position of the needle is again confirmed by the introduction of 2–4 cc. of roentgenographic contrast material. Under fluoroscopy, the material should be seen to diffuse freely around bowel loops.

Following placement of the needle, gas is introduced. Nitrous oxide is used, since it is nonembolic and not too rapidly resorbed. The gas tank is connected to a 100 cc. glass syringe by plastic tubing through a 3 way stopcock. A second length of tubing connects the 3 way stopcock with the needle. Gas is aspirated into the syringe and then injected through the needle; 800 cc./m.^{2} of gas is usually an adequate amount. During initial introduction of gas, the abdomen is palpated for possible subcutaneous crepitation and percussed to confirm the intra-abdominal location of the gas. After the calculated amount of gas is introduced, the needle is removed. The patient is placed in the prone position and secured with a shoulder holder and straps. The head of the table is lowered to a 45° angle with the patient's head down. The pelvis is shaken for optimal gas distribution.

The x-ray tube is then positioned in a perpendicular position to the floor ("zero degrees") over the pelvis, centering on the sacrococcygeal joint (Fig. 1), and a single roentgenogram is taken. After this roentgenogram is reviewed for technique and position, additional roentgenograms are taken in the oblique positions at "zero degrees." Films may be exposed with the tube positioned 10° cephalad and 10° caudad to the "zero position" to alter the angle of projection of the internal structures. Following the pneumogram, an in-

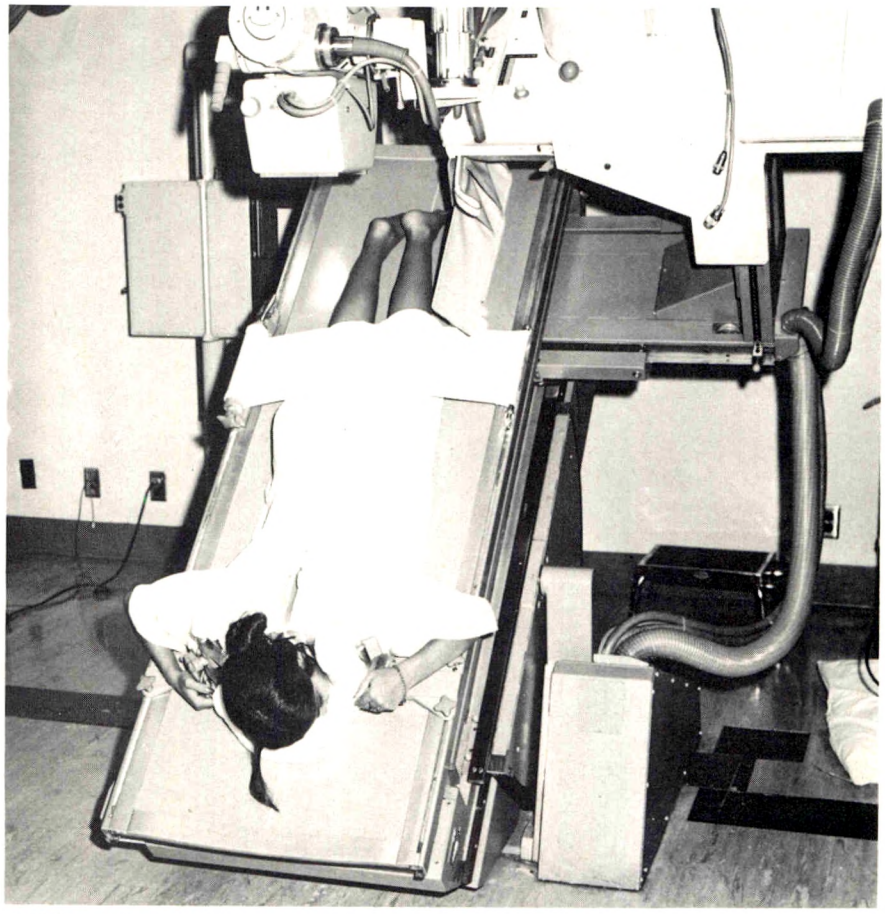

FIG. 1. The patient is positioned with the table at a 45° angle and the tube perpendicular to the floor. Note the shoulder rest, the padding and the strap.

travenous urogram is obtained in patients where the differential diagnosis includes abnormalities of adrenal function.

Complications of this procedure, reported in the literature[13] and in our series, have been few and minor. Occasionally, the tip of the needle is positioned outside the peritoneal cavity. This is easily confirmed by the introduction of the contrast material which forms a "pocket," if collected subcutaneously (Fig. 2*A*). Should this occur, the needle can be promptly repositioned (Fig. 2*B*). In a single case, prior to the use of contrast medium for needle placement, subcutaneous gas was detected by palpation after introduction of a small quantity of gas. Most older children complain of some discomfort in the right shoulder following the procedure, probably because of accumulation of gas under the diaphragm, but the discomfort rapidly abates following gas resorption.

STANDARDS FOR OVARIAN AND UTERINE SIZE

Weigen and Stevens[14] reported roentgenographic standards for normal adult ovarian size ranging from 2 to 4 cm. in length and 1.5 to 3 cm. in width. In our technique there is a magnification factor of 1.25. Based on this we calculated standards for the ovary of 2.5–5 cm. in length and 1.8–3.9 cm. in width. Measurements are taken directly from the films at "0" degrees. The size of the prepubertal ovary has been described in anatomic specimens,[11] but not specifically in the radiologic literature. However, it can be inferred from the anatomic data that the gland is smaller in

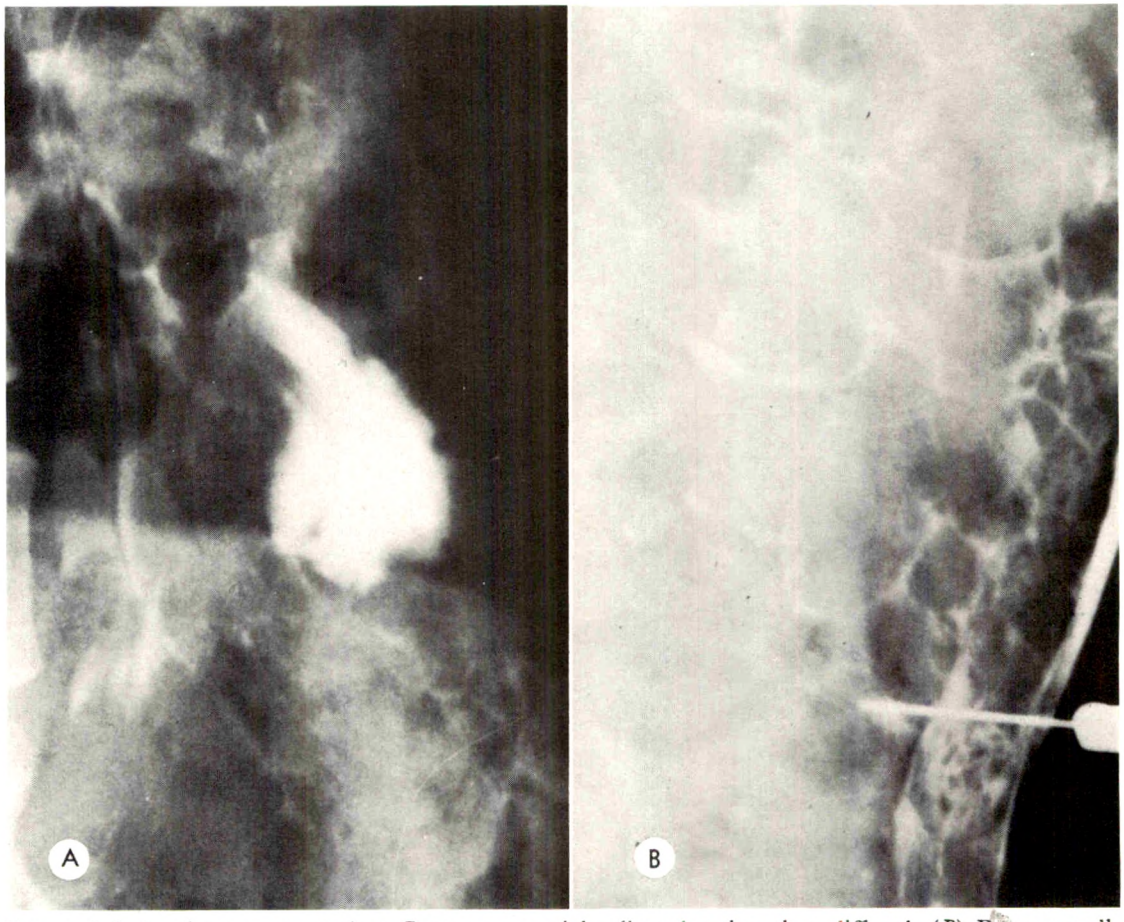

Fig. 2. (*A*) A subcutaneous pocket. Contrast material collected rather than diffused. (*B*) Proper needle position. The contrast material diffused freely between the bowel loops. Note that this was a case where we repositioned the needle after introducing a small amount of gas extraperitoneally.

the prepubertal patient who is not under gonadotropin stimulation. Uterine size for children has similarly been described by anatomic findings[3] and varies from 3.5 cm. in length in the first month of life (because of intrauterine hormonal stimulation), to a small structure of 2.5 cm. or less in length by 1 month. The size remains infantile until estrogen stimulation, during puberty, results in rapid enlargement to a width of 5–7 cm. and a thickness of 2 to 8 cm.[3] A representative study in a prepubertal patient is seen in Figure 3, and a normal pubertal study is seen in Figure 4.

RESULTS

The clinical information, laboratory data and roentgenographic findings in our patients are summarized in Table 1. The 46 patients are divided into 7 groups based on their initial clinical presentations. Of the 11 patients in whom the diagnosis of sexual precocity was entertained,[1] 1 had an ovarian neoplasm which was identified by pelvic pneumography (Fig. 5). Seven patients had pneumographic findings consistent with the clinical diagnosis of idiopathic isosexual precocity. Three patients who failed to show significant roentgenologic evidence of ovarian or uterine enlargement have subsequently been shown not to have isosexual precocity.

Four patients with gonadal dysgenesis were studied. A gonadoblastoma was iden-

tified in 1 patient (Fig. 6). The gonadal mass corresponds to an area of calcification seen on the scout roentgenogram. In contrast, the pneumogram of a patient with uncomplicated gonadal dysgenesis is shown in Figure 7.

Four patients with unexplained primary amenorrhea were studied. Two were found to have congenital absence of the uterus; pneumogram of 1 is shown in Figure 8. Of 3 patients with secondary amenorrhea, 1 had ovarian enlargement consistent with the diagnosis of polycystic ovary syndrome, and another had small ovaries consistent with hypogonadotropic hypogonadism. The third pneumogram was normal.

Ten female teen-age patients had as their principal complaints hirsutism with or without virilization. Of these, 5 had clinical or roentgenographic evidence of the polycystic ovary syndrome. The significant ovarian enlargement found in 1 patient is shown in Figure 9. Two patients

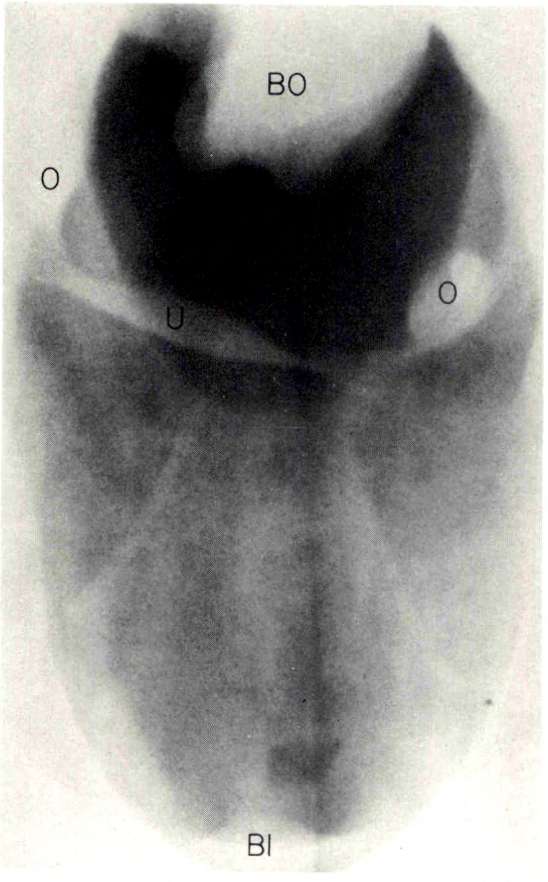

Fig. 3. Normal prepubertal pneumogram. BO = rectosigmoid colon; O = ovaries; U = uterus; Bl = bladder.

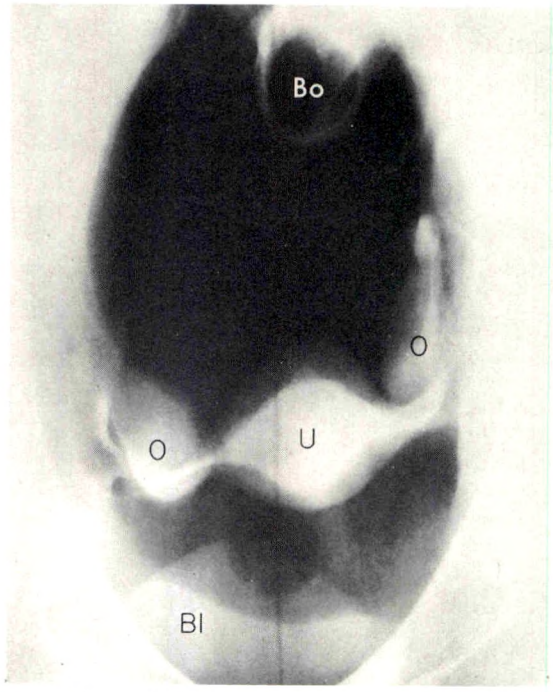

Fig. 4. Normal pubertal pneumogram. (Same abbreviations as in Figure 3.)

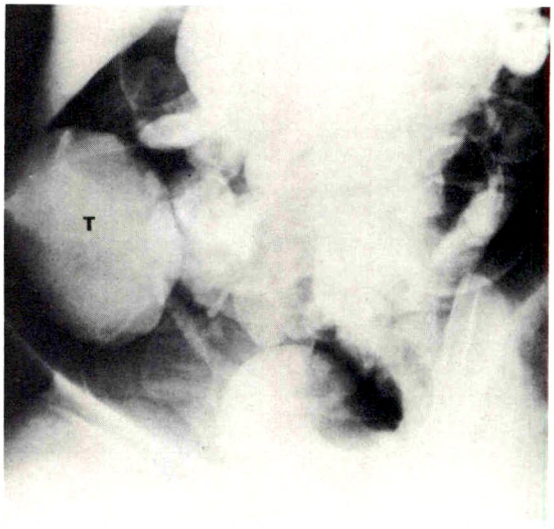

Fig. 5. Granulosa cell tumor of the right ovary. T = tumor. Note that the tumor was intrapelvic and connected to the right broad ligament. With the introduction of the pelvic gas it rose out of the pelvis and was palpable abdominally.

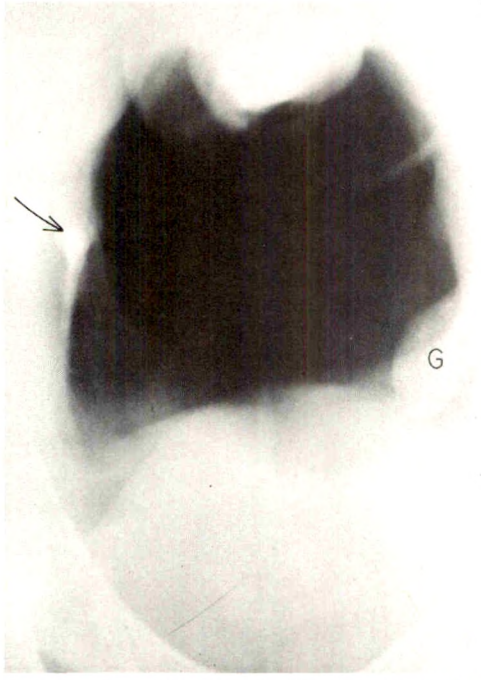

Fig. 6. Gonadoblastoma (G) on the left, with a typical small streak-like gonad on the right (arrow). Bladder covers the uterus.

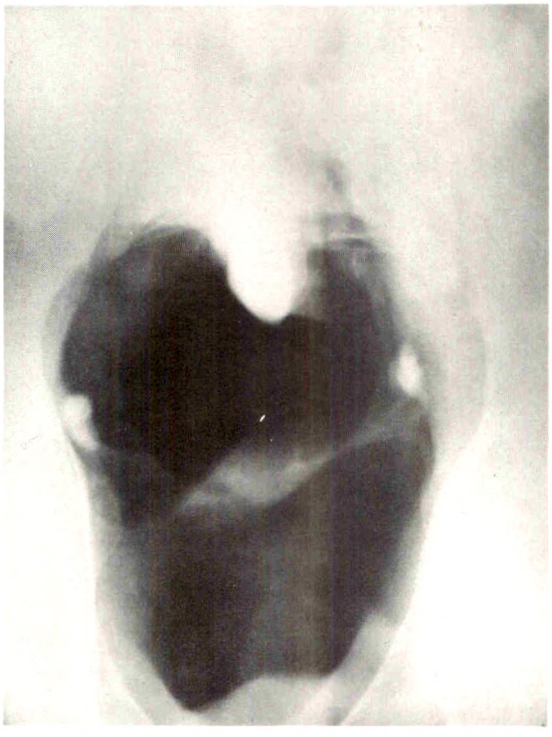

Fig. 7. Gonadal dysgenesis. Small characteristic ovarian streak-like structures.

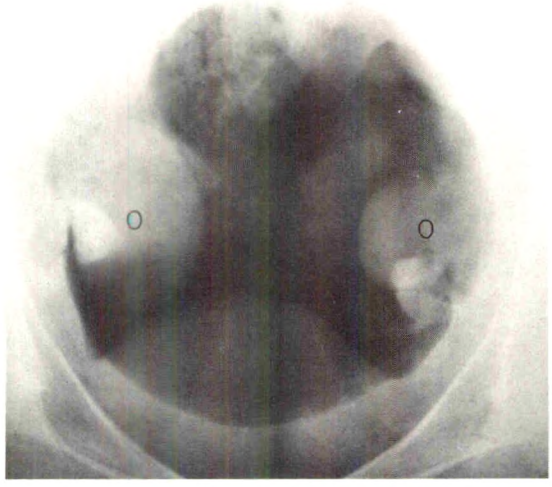

Fig. 8. Absent uterus and broad ligaments. Ovaries = O.

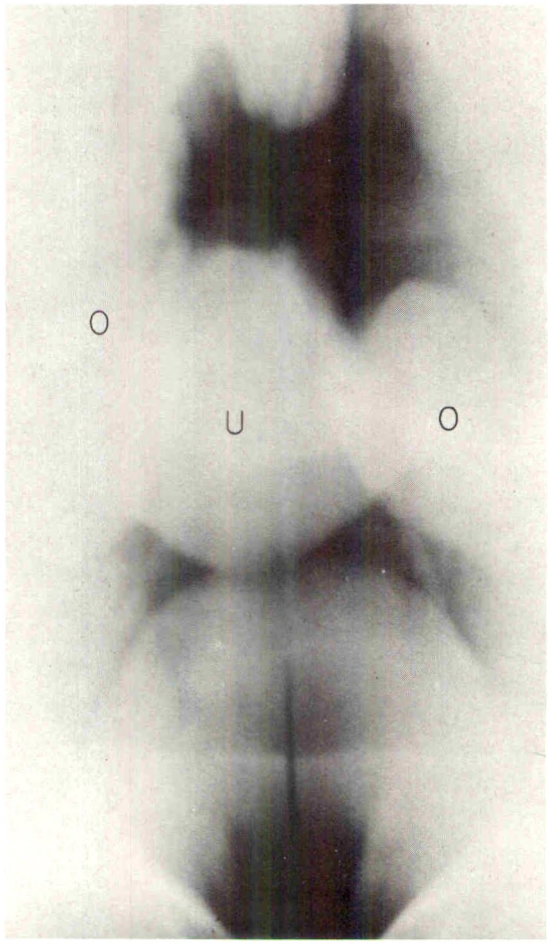

Fig. 9. Polycystic ovary syndrome. Very large ovaries that compress the uterus. O = ovaries; U = uterus.

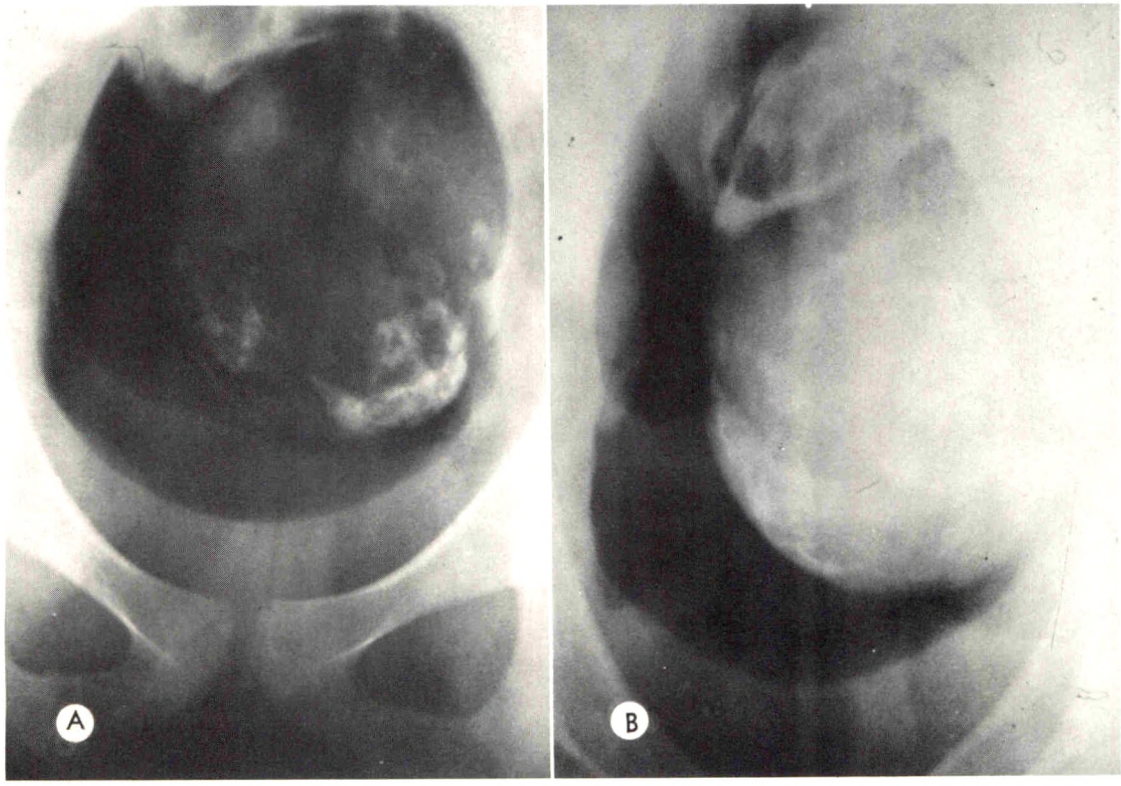

Fig. 10. (*A* and *B*) Pelvic pneumograms showing a large calcified ovarian tumor. This was not palpable on physical examination.

had adrenal tumors, presumptive evidence for which was shown on scout roentgenograms and intravenous urograms. One patient had a large, calcified pelvic mass identified as ovarian in origin (Fig. 10, *A* and *B*). Finally, in 1 patient we found significant uterine enlargement (Fig. 11) and subsequently confirmed the presence of a previously unrecognized and denied pregnancy.

Nine patients were evaluated because of the diagnosis of pseudohermaphroditism, in order to clarify the nature of the internal structures. One, with nonprogressive intrauterine virilization of her external genitalia and absence of the vagina, was shown to have normal female internal structures and was spared a planned exploratory laparotomy. Another with an absent vagina was shown to have an absent uterus but normal sized ovaries. The procedure was equally useful in a teen-age phenotypic male with hermaphroditism in whom the question of the presence of pelvic uterine or gonadal structures was raised. No structures were identified on pneumogram and their absence was confirmed by laparotomy.

Five patients were examined primarily to rule out diagnoses made by referring physicians. These ranged from operative reports of "absent internal structures" to the alleged surgical removal of "all pelvic organs." Finally, 1 patient was told that she had had cystic ovarian structures identified at prior exploratory laparotomy, and this indeed was confirmed.

DISCUSSION

Pelvic pneumography is a most valuable diagnostic procedure for the evaluation of children and adolescents with certain kinds of disorders of sexual development. The procedure has obviated the necessity for exploratory surgery in several patients, while making surgical intervention mandatory in others. At our institution the

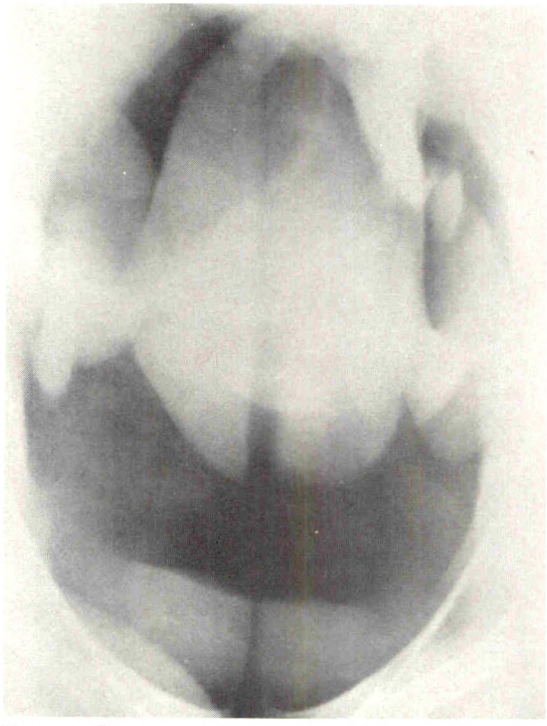

Fig. 11. Large, gravid uterus, which may be compressing the ovaries and is impinging on the rectum.

procedure has been performed with few complications, none of which has been serious.

Cooperation between the endocrinologist and the radiologist is prerequisite for securing the maximum information from the procedure. Additional procedures such as bimanual pelvic examination, a Papanicolaou's smear, cystography or vaginography, and funduscopic examination can be performed at the same time. In addition, in some selected cases, peritoneoscopy may be combined with pneumography in order to achieve even more information. Peritoneoscopy or pelvic laparoscopy alone have been used by others to obtain similar information, but the efficacy and applicability of this technique to young children have not been evaluated. The choice of technique will obviously depend on the availability of interested, skilled personnel. Under certain circumstances, peritoneoscopy may prove superior because of direct visualization of the structures and the possibility of obtaining material for biopsy. On the other hand, the procedure is much more invasive and is possibly more hazardous and difficult in small children.

Our roentgenographic findings have correlated well with the subsequent clinical courses and pathologic findings in our patients. Congenital absence of the uterus, presence or absence of the ovaries, broad ligaments and the uterus, ovarian neoplasms and enlarged ovaries can be identified with confidence. In addition, identification can be made of the presence or absence of certain anatomic structures prior to surgery. In patients with gonadal dysgenesis, where the question of gonadoblastoma formation is of importance[10] (those with a Y or presumptive Y in the karyotype), this procedure may serve to confirm the presence or absence of a gonadal mass.

The major limitations of pelvic pneumography are inherent in its gross radioanatomic nature. Neither histology nor hormonal function can be gleaned from pneumograms. In some cases of intersex, for example, a pelvic gonad may be identified, but its functional elements can not be recognized (as in an ovotestis). In cases with enlarged ovaries compatible with the polycystic ovary syndrome, the presence of an ovarian neoplasm within one of the ovaries cannot be ruled out.[15] Thus, while the procedure is most useful in many circumstances, it may have limited value in others.

SUMMARY

Pelvic pneumography has been performed in 46 children and adolescents over a 4 year period.

The patients were grouped into 7 categories based on their initial clinical presentations: sexual precocity; gonadal dysgenesis; primary amenorrhea; secondary amenorrhea; hirsutism and/or virilization; pseudohermaphroditism; and previously unclear diagnoses.

Pneumography was useful in characterizing ovarian and uterine size, identifying ovarian neoplasms and polycystic ovaries,

and determining the presence or absence of the uterus and gonads.

The technique is described in detail and noted to be largely free of complications. Based on our experience its wider use in the evaluation of complex endocrine and gynecologic disorders in children is recommended.

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DOUBLE CONTRAST KNEE ARTHROGRAPHY IN CHILDREN*

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CHILDREN'S knees can be studied by double contrast arthrography just as in adults. The paucity of information in the literature regarding pediatric knee arthrography stimulated a review of our experience in 24 children less than 12 years old. Compared to adults, the incidence and types of arthrographic abnormalities in children are unique.

MATERIAL AND METHOD

Twenty-four, or about 1 per cent, of slightly more than 2,500 arthrograms obtained in the last 4 years (1969–1973), were studies of children 4 to 12 years of age. The 7 girls and 17 boys underwent either surgical confirmation or clinical follow-up. A review of teenage arthrograms (ages 13 through 19), showed that the indications for arthrography, the lesions found, and the technique were the same as in adults, so that they did not warrant independent study and analysis.

TECHNIQUE

The arthrographic technique is similar to the double contrast method used in adults.[1] Reassurance and gentle restraint of the patient during injection were sufficient to allow adequate examination of all the children. Neither heavy sedation nor general anesthesia was needed. The knee to be examined was extended and taped to a splint (Fig. 1, *A* and *B*). Both knees and the splint were then securely fastened to the x-ray table with adhesive tape. A restraining tape was placed across the child's chest to prevent sitting up during the injection (Fig. 1, *A* and *B*). This helped to relax the quadriceps muscle which allowed easier insertion of the needle behind the patella. An assistant reassured the child. It was not necessary for anyone to hold the knee and the sterile field was not disturbed.

After sterile preparation and draping, 1 per cent Lidocaine was injected into the skin just medial to the middle third of the patella. The tip of the needle was positioned behind the middle of the patella and contrast material and then air were injected. Modifications of the adult injection technique were: (1) the use of a 23 gauge, 1 inch needle for injection; (2) only 1½ cc. of 76 per cent meglumine diatrizoate;* and (3) only 10 to 15 cc. of air to fill the comparably smaller joint of a child. Air was injected until the radiologist felt mild resistance. Glass syringes were preferred over plastic since they provided a greater sensitivity to resistance during the injection. After the injection, the needle was withdrawn and the straps removed. The knee was flexed 3 times to distribute the contrast material throughout the joint and the study was then continued in the same manner as with an adult knee.[1,4]

RESULTS

The normal pediatric knee arthrogram is similar to the adult with only a few exceptions. All the articular cartilages in the child's knee are thicker than in the adult. The younger the child, the thicker the cartilage. The menisci have an adult configuration but are proportionately smaller (Fig. 2, *A* and *B*; and 3, *A* and *B*).

Eleven studies were normal and 13 abnormal. No postexamination complications developed. Of the 11 patients with normal arthrograms, 8 were treated conservatively and are symptom free on clinical follow-up between 6 and 40 months. One 6 year old

* Renografin-76, E. R. Squibb and Sons, Inc., P. O. Box 4000, Princeton, New Jersey.

* From the Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri.

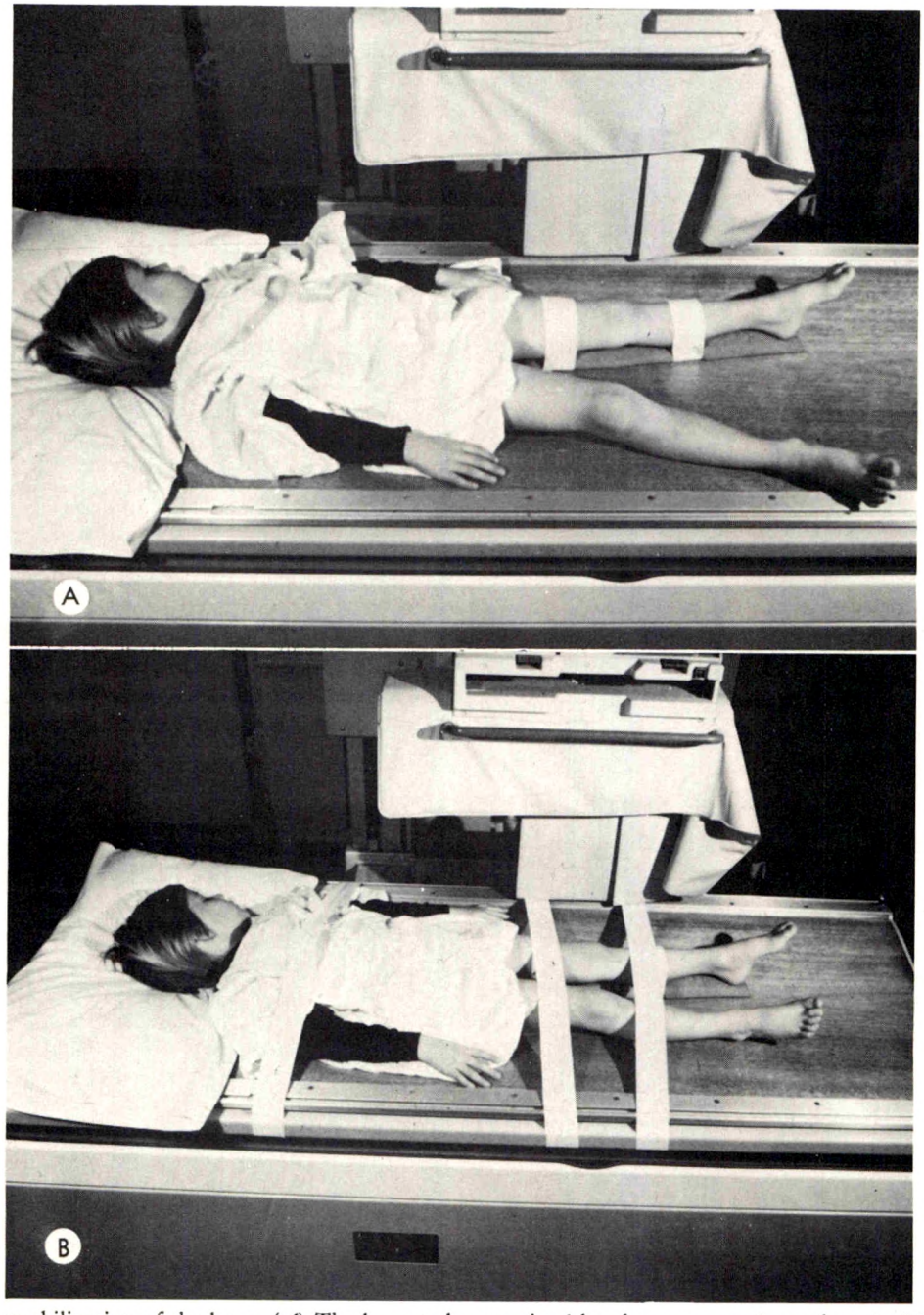

Fig. 1. Immobilization of the knee. (*A*) The knee to be examined has been strapped to a board with 2 inch tape. (*B*) Restraining tapes are then additionally placed across both knees and the chest.

with a normal arthrogram was felt to have a medial collateral ligament strain. A year later his pain and medial collateral ligament tenderness persist. Another patient with a normal arthrogram underwent surgery 3 days later. He had only a hemarthrosis with normal ligaments and cartilages, while a biopsy of the synovium showed chronic synovitis. A year later his symptoms subsided. The other patient with the normal study has been followed for 2 months and is becoming symptom free.

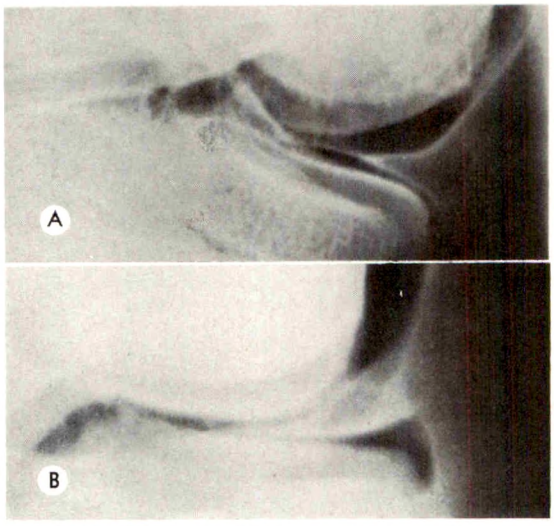

Fig. 2. (*A*) Normal medial, and (*B*) lateral meniscus in a 10 year old child. The articular cartilages are thicker than in the adult. The menisci have an adult configuration.

Three types of lesions form the bulk of the pathologic conditions, namely, discoid lateral meniscus, osteochondritis dissecans, and tears of the lateral meniscus. The 3 patients with discoid meniscus all underwent surgery which confirmed the roentgenographic diagnosis (Fig. 4, *A* and *B*). The symptoms of these 3 patients have resolved following excision of the involved meniscus.

The 4 patients with osteochondritis dissecans have been followed conservatively without surgery and are presently filling in their defects. The torn lateral menisci of 2 patients were confirmed and resected at surgery. These 2 patients are now asymptomatic. One 11 year old with an arthrographically demonstrated torn lateral meniscus was not operated upon and is now symptom free. One 11 year old child with a hemangioma of the knee joint has been previously reported (Fig. 5).[3,11]

One patient with disuse atrophy following derotational osteotomies of the femur had an underdeveloped patella with decreased ossification. Another patient with spondyloepiphyseal dysplasia had palpable masses about the patella in both knees suggesting loose bodies. Arthrography demonstrated a projection of non-ossified articular cartilage extending from the superior pole of each patella (Fig. 6). The patient was not operated upon, since this abnormality was not considered the cause of the patient's symptoms.

DISCUSSION

Congenital or developmental abnormalities constitute over half of the arthro-

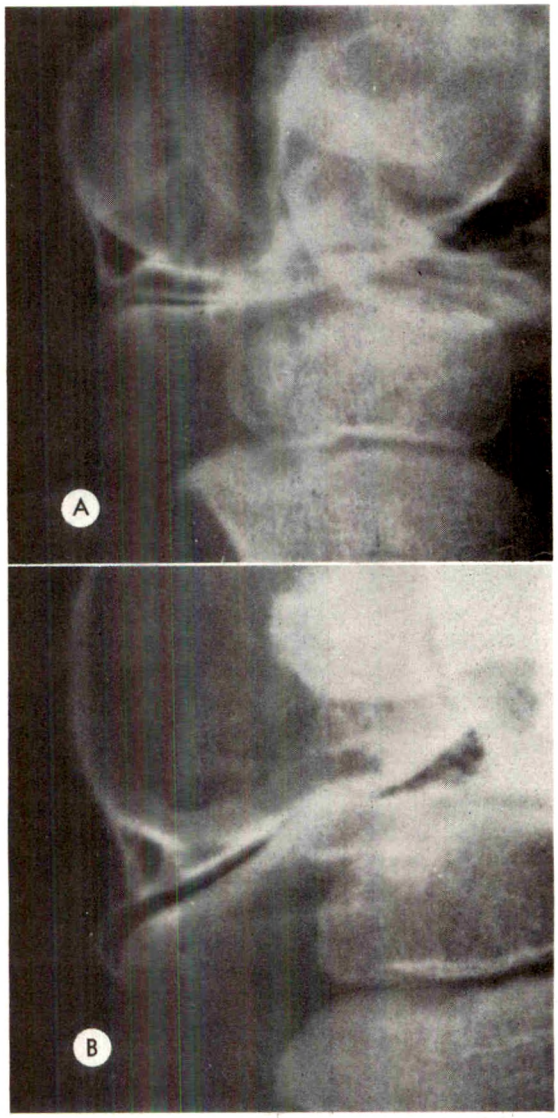

Fig. 3. (*A*) Normal medial meniscus and (*B*) lateral meniscus in a 3 year old boy. The articular cartilages of the femur and tibia are even thicker than those of the patient in Figure 2. The menisci have an adult configuration.

graphic abnormalities found in our series. Discoid meniscus, tears of the lateral meniscus, and patellar abnormalities are all secondary to either developmental or congenital factors.

The pathogenesis of a lateral discoid meniscus is not entirely settled. Certain authors originally felt that the discoid meniscus was an intrinsic congenital deformity.[2,7,10] However, Kaplan,[5] in an impressive embryologic and comparative anatomy study, concluded that the discoid meniscus was never found in the human fetus, but rather is acquired after birth as a consequence of congenital alteration in the attachment of the posterior horn of the lateral meniscus.

The normal lateral meniscus is attached to the tibia at the anterior and posterior aspects of the lateral intercondylar tubercle and to the femur by the meniscofemoral ligament or the ligament of Wrisberg. According to Kaplan,[5] patients who develop a lateral discoid meniscus lack a posterior attachment from the meniscus to the tibial plateau. During knee extension, the posterior meniscus horn dislocates into the intercondylar notch where it is held by the meniscofemoral ligament. As the knee flexes, the meniscus is pulled laterally by the coronary ligaments and popliteus tendon. Therefore, Kaplan[5] postulates that the normal horn is trapped between the tibia and the femur and becomes thickened into a discoid meniscus. The discoid meniscus is an uncommon orthopaedic condition, most often discovered in children. It causes a clicking sensation during extension. Occasionally, the knee may lock and some authors feel that the discoid meniscus is more susceptible to tears than a normal meniscus.[6]

Roentgenographically, in place of the normal triangle, the discoid meniscus free margin bulges into the interarticular space in an oblong fashion. It is often torn and may be fragmented. If severely fragmented, it cannot be differentiated on occasion from an extensive tear with displacement of the

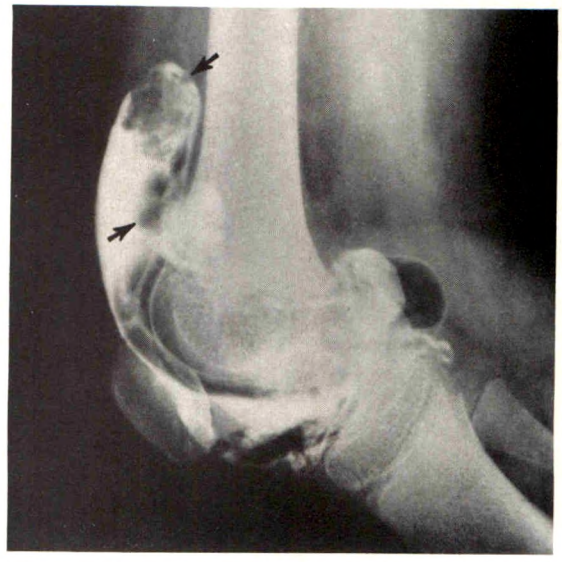

Fig. 5. Hemangioma of the knee joint. Multilobulated mass occupying the apex of the suprapatellar bursa.

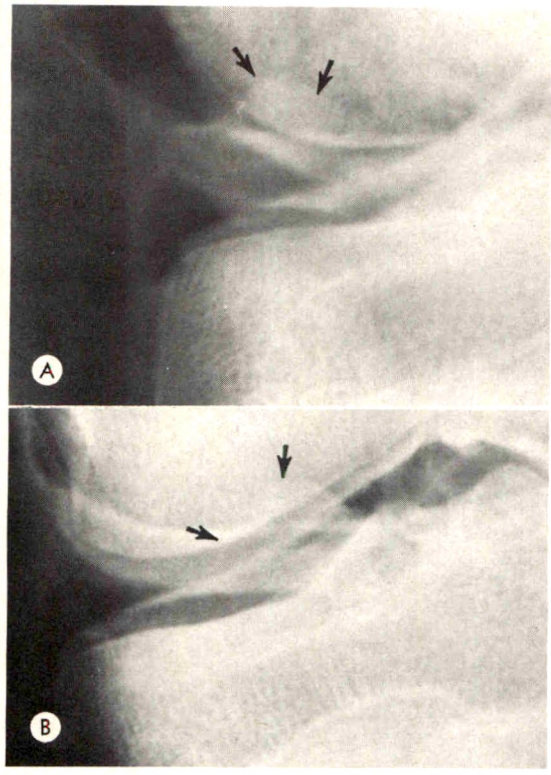

Fig. 4. Discoid lateral meniscus. (*A*) The apex of the anterior and (*B*) middle thirds of the meniscus are bulbous. The body of the meniscus extends well into the intercondylar notch. The lesion was surgically confirmed.

Fig. 6. A cartilaginous spur extends above the upper pole of the patella. This clinically simulated a loose body.

free fragment into the intercondylar notch.

All 3 patients with a torn menisci had involvement of the lateral meniscus (Fig. 7). This is in contrast to the situation in adults where a majority of tears present in the medial meniscus. The mechanism of meniscus tears has been the subject of extensive research and speculation. Rotational compression forces of the femoral condyle on the menisci during movement and stress result in cartilage tears. Most commonly in the adult, the medial meniscus is torn as the foot is held fixed in place and the femoral condyle rotates externally on the tibia. The normal adult usually has no varus or valgus deformity. On the other hand, children between the ages of 2 and 12 have varying degrees of genu valgus as a normal part of the growth process. After age 12, this valgus deformity is corrected by normal growth.[9] Perhaps the higher incidence of lateral meniscus tears in children is related to altered weight bearing and rotational forces transmitted to the lateral meniscus rather than the medial during the valgoid stage of normal knee development.

The diagnosis of osteochondritis dissecans usually is evident on the plain roentgenograms. Arthrography may be of help in demonstrating the condition of the cartilage overlying the necrotic bone or to establish that meniscus injuries may or may not contribute to the symptoms. The articular cartilage of the femoral condyle can be evaluated to establish whether it merely bulges from the underlying bone, is fractured and nondisplaced, or presents as a loose fragment in the joint. It is essential to demonstrate the overlying articular cartilage with a roentgenographic beam projected tangentially to the area of aseptic necrosis. The plain roentgenogram can establish the location of the lesion in relation to the anterior, middle, or posterior third of the condyle. If the lesion is in the middle third of the knee, it will be projected adequately on the standard arthrographic spot roentgenograms of the menisci. If it is located posteriorly, a vertical beam can be projected tangential to the posterior third of the femoral condyle when the patient is placed supine and the hip and knee are flexed (Fig. 8). The femoral condyle can be slightly rotated to obtain the maximal projection of the area of osteochondritis dissecans (Fig. 9).

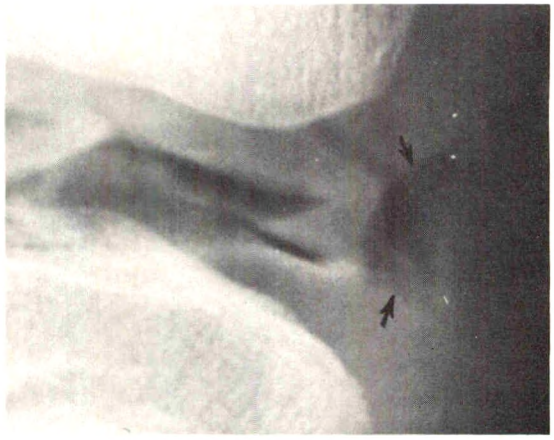

Fig. 7. Tear of the lateral meniscus. The meniscus has been separated from the joint capsule. The space between the meniscus and the capsule is not the popliteus tendon bursa.

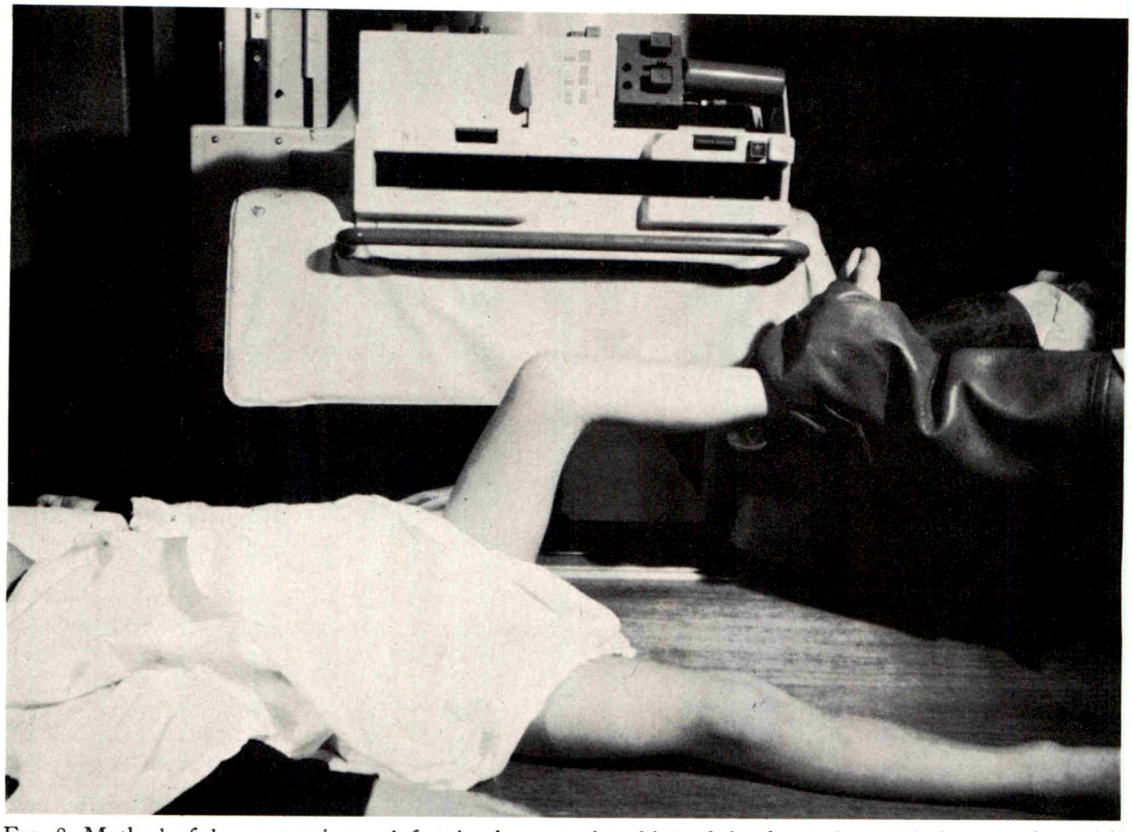

Fig. 8. Method of demonstrating a defect in the posterior third of the femoral condyle in osteochondritis dissecans. The knee is flexed at 90 degrees and the beam projected along the posterior surface of the femoral condyle.

In regard to lateral meniscus tears, our results are similar to those of the extensive study of knee arthrography in children carried out by Stenstrom.[12] Forty-eight per cent of his patients had tears of the lateral meniscus, which is much greater than in the adult knee. Stenstrom studied patients between ages 1 and 18 years. A great majority of them were older than age 12 and it was impossible to determine whether an even larger percentage of those patients under age 12 may have had lateral rather than medial meniscus tears.

The indications for pediatric knee arthrography differed somewhat from adults. However, in general, arthrography is used to exclude intra-articular causes of abnormal joint motion. Its value in trauma is demonstrated by the patients in this group with torn lateral menisci. In osteochondritis dissecans, the location of any loose articular cartilaginous bodies, and the exclusion of any additional lesions becomes important. Gait disturbances in children may be caused by intra-articular lesions, but are more likely to be the result of neuromuscular or growth disturbances such as cerebral palsy, congenital dislocation of the hip, or unequal leg length. Knee locking is a rare occurrence in children and may be caused by extra-articular lesions. We have been impressed by the locking which may be occasioned by fibrosis of the rectus femoris muscle which can prevent full flexion. A 4 year old child recently referred to us for arthrography had in reality fibrosis of the rectus femoris muscle as the result of multiple intramuscular antibiotic injections during treatment for a prolonged severe systemic infection.[8]

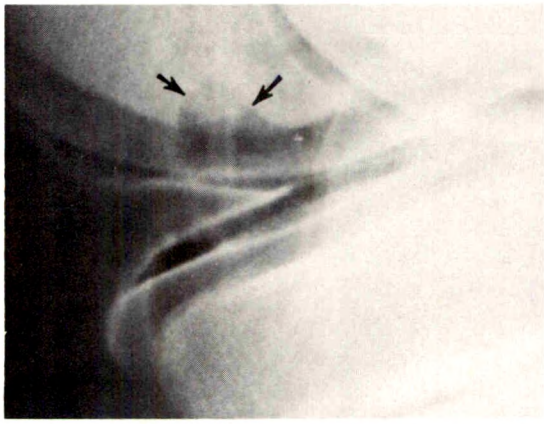

Fig. 9. Osteochondritis dissecans (arrows). The articular cartilage overlying the defect is intact.

SUMMARY

Knee arthrography in the pediatric patient can be performed without heavy sedation or general anesthesia.

Lateral meniscus tears predominate over those of the medial meniscus. The most common lesions found are tears of the lateral meniscus, osteochondritis dissecans, and lateral discoid meniscus. Congenital or developmental factors apparently contribute to half of the demonstrated lesions.

Extra-articular causes should be sought in the very young child with a locked knee.

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VOL. 123, NO. 4

LATE ONSET OF SUBCUTANEOUS CALCIFICATIONS AFTER INTRAVENOUS INJECTIONS OF CALCIUM GLUCONATE*

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INTRAVENOUSLY administered calcium gluconate has been used for more than 40 years in the treatment of neonatal tetany. A greater appreciation that calcium injections are often needed by infants of low birth weight or with neonatal asphyxia has increased the frequency of use of these preparations.[7] Since the route of administration was changed from intramuscular to intravenous in the 1940s no complications have been reported.

We present 11 infants who had the late onset of local reactions after intravenous calcium gluconate administration. The reactions consisted of peripheral nodules, cellulitis and roentgenographically visible calcifications of soft tissue and veins.

CLINICAL MATERIAL

Clinical features of the 11 infants are presented in Table 1. None had any indication of extravasation at the time of injection. Calcium gluconate was given intravenously as a 10 per cent solution, 200 mg./kg. every 6 to 8 hours either as a single injection, while the heart was auscultated, or by infusion. Indications for therapy included tremors, convulsions, hypocalcemia or apneic spells associated with serum calcium levels below 7.5 mg./100 ml. Local skin and subcutaneous lesions appeared always at the site of a previous peripheral intravenous injection. In 5 infants, these presented as subcutaneous nodules (Fig. 1), while in the remaining 6, cellulitis occurred with erythema, tenderness, warmth and fluctuation. The average duration between the first day of calcium injection and the appearance of the lesion was 13 days.

Five infants had incision and drainage and 1 other had needle aspiration of the areas of cellulitis and abscess. White granular material and blood clots were removed from all these lesions. In only 1 patient was a positive culture (*Staphylococcus aureus*) obtained. Six patients were treated with either intravenous methicillin or oral oxacillin, 200 mg./kg./day. Four infants had neither surgery nor systemically administered antibiotics. The inflammation disappeared in all 11 infants. Two infants died.

ROENTGENOGRAPHIC FINDINGS

In all infants, roentgenograms obtained

FIG. 1. Firm subcutaneous nodules with induration and brownish discoloration of the overlying skin.

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TABLE I

SUMMARY OF CASES

Case	Location	Duration, Therapy (days)	Delay in Appearance of Lesion (days)	Outcome
1. D.P.	Medial aspect of mid leg	5	20	Minimal skin induration present at 4½ months, radiographically clearing in 2 months
2. G.S.	Dorsum of left hand, left frontal region	3	14	Clinical and radiologic resolution at 3 months
3. F.S.	Right hand and wrist	1	3	Inflammatory reaction subsided within 10 days
4. L.J.	Left anterior cubital fossa	1	7	Radiologic resolution at 1 year
5. S.G.	Distal part of left leg	1	19	Inflammatory reaction subsided in 2 weeks, radiographic clearance in 3 months
6. T.A.	Dorsum of right ankle, left medial malleolus	2	11	Calcification cleared in 1 month
7. M.D.	Dorsum of left hand	2	11	Induration and calcification resolved in 1 month
8. K.M.	Left forearm	Intermittent for 60 days	Undetermined	Clinical and radiologic lesion present at time of death
9. E.L.	Dorsum of right wrist	Intermittent for 60 days	Undetermined	Subcutaneous mass and calcification present at time of death, had coagulase, positive *Staphylococcus aureus*
10. S.A.	Left foot	1	14	Resolution at 2½ months
11. A.A.	Right wrist and forearm	1	14	No follow-up

at the time a lesion was first noticed showed soft tissue calcification at the site of the palpable mass (Fig. 2). Calcifications, even when extensive, never involved either the overlying skin or the periosteum of adjacent bone (Fig. 3; and 4, *A* and *B*). In 4 infants, the entire cephalic vein was also calcified; in 2 of them, the calcification had changed from solid to a venous pattern over a period of weeks. In 7 of the 9 infants with follow-up roentgenograms, the calcification completely resolved between 1 month and 1 year of age (Table 1). In the remaining 2, calcification was still present at time of death at ages 5 weeks and 3 months, respectively.

DISCUSSION

The roentgenographic appearance of a large calcified subcutaneous mass can be alarming until the history of preceding calcium gluconate infusion is obtained. Treatment of such an area is simplified by its recognition as a complication of calcium

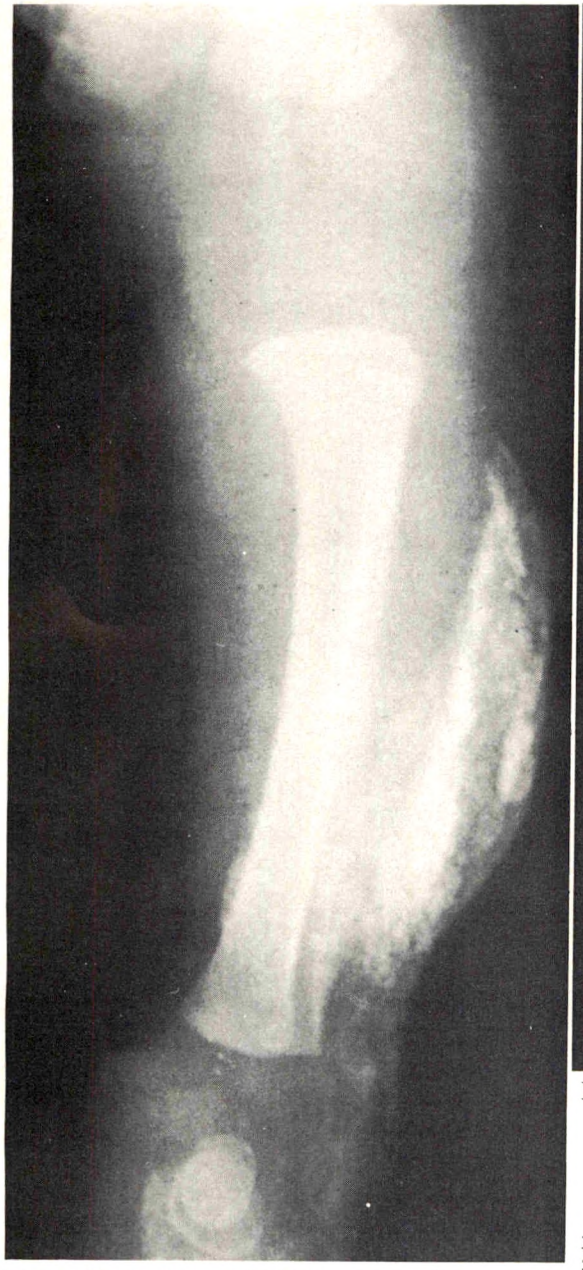

Fig. 2. Extensive calcification on lateral aspect of lower extremity which extended subcutaneously to dorsal aspect. The tibia and fibula were intact.

Fig. 3. Amorphous calcification of dorsum of hand and wrist at site of injection performed 2 weeks previously.

gluconate injection. The swelling is best managed conservatively, with needle aspiration done only if necessary to differentiate it from a pyogenic abscess.

Experimental studies have shown that necrosis induced by subcutaneous or intramuscular injection of calcium is followed in 3 to 5 weeks by calcification, with more calcium deposited than injected.[3,5] In one study, for example, calcium plaque formation along fibrous elements and blood vessels was 100 times the amount injected.[3] Injured tissue took up calcium resulting in a fall in serum calcium.[4] When calcium gluconate was injected subcutaneously into rabbits, calcification in the subcutaneous tissue, muscles, and walls of arteries and veins was histologically visible at 8

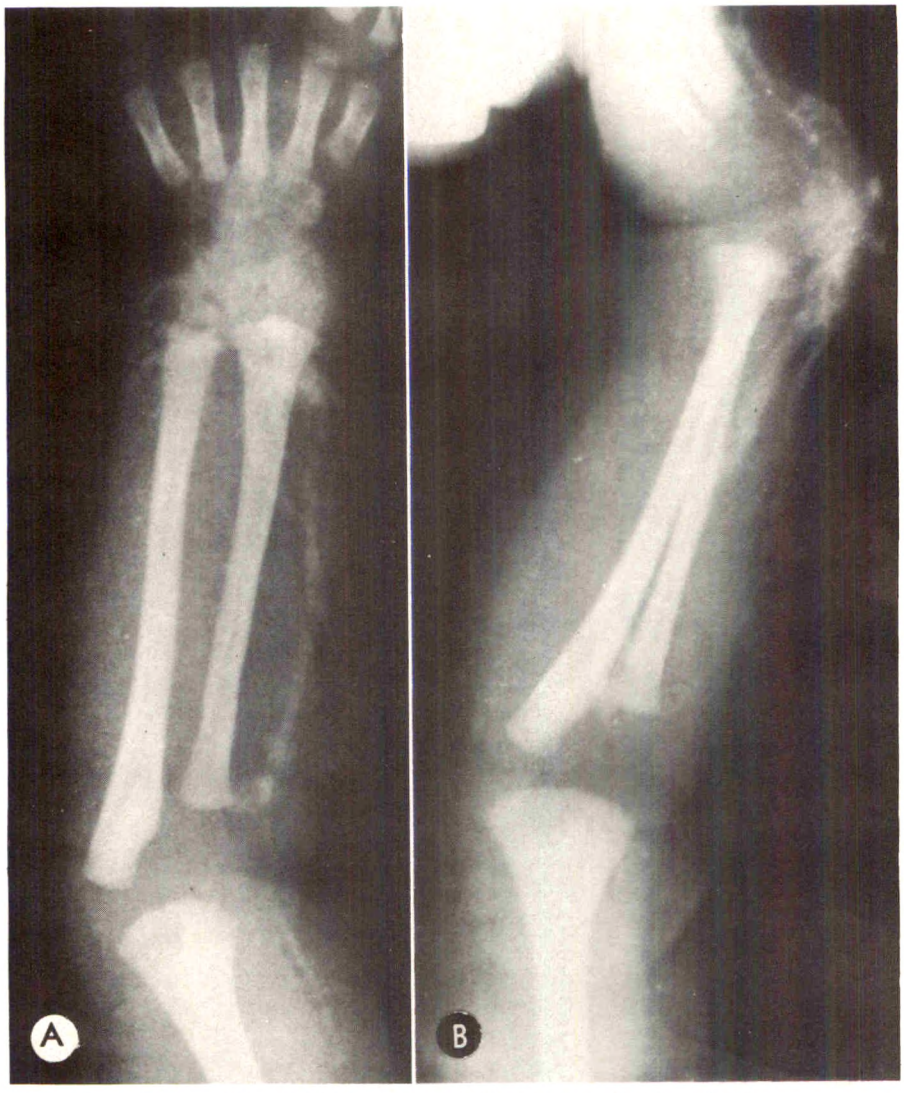

Fig. 4. (*A* and *B*) Extensive calcification at dorsum of wrist extending in a venous pattern along hand and forearm.

days, while roentgenographic evidence of calcification was maximum at 2 weeks and gone by 6 weeks.[1]

CONCLUSION

In our series, the complete absence of skin sloughs is evidence against any injections having been mistakenly made intramuscularly or subcutaneously Our experience suggests, instead, that vascular leakage not clinically visible is sufficient to produce these findings. The rapid injection of calcium gluconate caused transient hypercalcemia. Areas injured by previous attempts at starting intravenous injections, perhaps accompanied by residual local hematomas, may have acted as niduses for calcium deposition.

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THE AMERICAN JOURNAL OF ROENTGENOLOGY RADIUM THERAPY AND NUCLEAR MEDICINE

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Fifty-seventh Annual Meeting: Americana Hotel, San Juan, Puerto Rico, May 4–9, 1975.

EDITORIALS

INFORMATION RETRIEVAL

ONE SUCCESSFUL METHOD FOR CONTINUING MEDICAL EDUCATION

THE conscientious physician attempting to be well informed is confronted by an ever increasing current literature, both in terms of size and numbers of journals. If, like most of his colleagues, he has something less than total recall, a method for rapid information retrieval is mandatory. Recent papers[1,2,3] clearly show that to be successful, any system should be rapid, comprehensive, inexpensive, personalized and yet almost effortless. Such a system used satisfactorily during the last seven years is based on the American College of Radiology Index for Roentgen Diagnoses.[4]

System Design. The key to an effective information retrieval system is a comprehensive index.[5] Any may be used, for example: the index of a major textbook or an abbreviated Index Medicus. Radiologists are fortunate in that several radiologic diagnostic classifications exist,[6] which, with modifications, provide an excellent beginning that may be expanded in the users' areas of special interest. I use the readily available American College of Radiology (ACR) Index for Roentgen Diagnoses. The information is most conveniently stored in a filing cabinet with suspension files such as the Pendaflex system. This keeps the folders orderly and insures rapid access. For impecunious trainees, simple cardboard files supplied by mail order houses[7] are adequate.

Using the American College of Radiology Index, suspension folders are cut in two to serve as the major category headings. Separate intact folders are created for each of the subcategories of the major anatomic divisions. Additional categories such as for ultrasound, nuclear medicine, or administration, with subheadings, can be introduced at any time with appropriate modification of the index and file. Color coding is optional, but speeds retrieval.

Procedure. Journals may either be saved or ripped apart. I save and bind the major radiology journals and rip the weekly general medicine publications. Some may find it handier to have duplicate subscriptions, one to bind and another to rip. Compared with other costs of medical education, such as attending meetings, this is not so extravagant as it first seems. Ripped out articles, reprints, and notes of lectures and discussions are simply coded in the upper right hand corner and filed. Articles in bound or to-be-bound journals are copied. Since the first page of an article frequently has the summary, xeroxing this page alone usually is all that is necessary. When researching a topic, these first sheets serve as a bibliography and quick data base. Articles of greater interest or those that may be needed quickly (such as the description of therapy for a particular complication) are copied in their entirety and placed in the file. Reprints are only obtained when better quality radiographs than that produced by copying machines are desirable. A first

[1] Felson, B., and Feltham, C. A simple method of information retrieval. *Radiology*, 1972, *105*, 315–318.

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[5] Index Organization for Information Retrieval. GC 20-8062-1, White Plains, N. Y., IBM Corp. (Technical Publications Dept.) 2nd Edition, 1961.

[6] Kovisto, E. Comparative study of roentgen diagnostic classifications. *Acta radiol.* 1969, Suppl. 285.

[7] Accountants' Supply House, 518 Rockaway Avenue, Valley Stream, New York 11582.

page copy is always placed in the file in case the requested reprint is unavailable. For the infrequent coding conflict, duplicate face copies may be placed in 2 file folders. Culling of unwanted or out-of-date information is simply performed whenever the folder is reviewed.

Much has been recently written questioning the effectiveness of traditional methods of medical education.[8,9] It is obvious that the emphasis must shift toward the skillful obtaining of information rather than on memory retention. Some thoughtful educators believe the most productive learning experience for physicians is achieved by solving a particular patient care problem, rather than attending courses of a prescribed number of hours.

[8] Rosenberg, E. W. Who's out of date? Editorial. *N.E.J.M.*, 1971, *284*, 850–851.
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CONCLUSION

Information is only useful if available. The system described has effectively served as a rapid, economical and painless method of information retrieval for continuing medical education and patient care.

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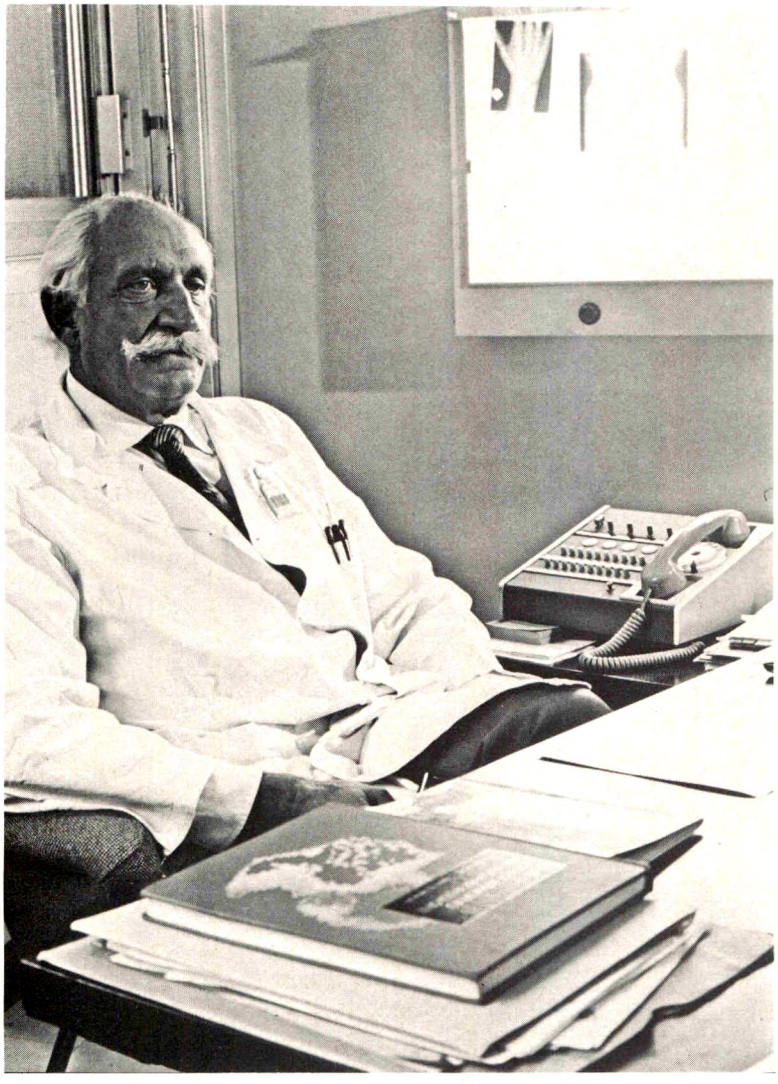

JACQUES LEFÈBVRE
1907-1974

CLOSE to his beloved second home in Boulogne sur Seine, while on a walk in the woods of Fontainebleau, Jacques Lefèbvre suddenly collapsed and died on November 10, 1974. On that day pediatric radiology lost one of its most endearing and influential figures.

Professor Lefèbvre was born in LeHavre and received his premedical and medical education in Paris. He was initially interested in pediatrics, but after an internship he changed his orientation towards electrophysiology,—electro-physiotherapy—and radiology. He became a resident in these specialties, then combined, in 1938 and by 1943 had reached the grade of "Electroradiologiste des Hôpitaux." By 1946 he was in charge of his own department at the Hôpital Saint Vincent de Paul. In 1948 he was made chief of the department of ra-

diology at the leading pediatric institution in France, the Hôpital des Enfants Malades. In 1958 he was promoted to an associate professorship, and in 1968 he was named to one of the few full professorships in radiology at the medical school of the University of Paris. One of his proudest days was in 1972 when his department moved into its own modern quarters.

Doctor Lefèbvre and his associates made scientific contributions virtually throughout pediatric radiology. He was particularly interested in the central nervous and skeletal systems. He created a team of congenial younger colleagues, who supported and continued his work with confidence and enthusiasm. Evidence of this is the recent publication, under his senior editorship, of the first volume of *Radiopédiatrie*, which is also volume XVIII of *Traité de Radiodiagnostic*.

Jacques Lefèbvre was truly the creator of pediatric radiology in France. His influence goes far beyond the borders of his own country; former students hold important positions in the United States of America and Canada. Several of his trainees eventually became full professors and heads of departments of general diagnostic radiology in Paris and elsewhere. He was very active over many years in the planning and carrying out of the Paris Postgraduate Radiology meetings, by which many of his friends contributed to the training of radiologists at all levels.

One of his most far-reaching achievements followed from the rapport he attained with his professional peers in North America. In 1960, after a week in Boston, he attended the meeting of the Society for Pediatric Radiology in Atlantic City. The bonds originating there grew into long and rewarding friendships. Largely because of the enormous impression made on him by this meeting, the groundwork was laid for the formation in 1962 of the European Society of Pediatric Radiology. Professor Lefèbvre and his colleagues, particularly Jacques Sauvegrain and Clément Fauré, realized how much there was to be gained from regular contacts with co-workers in North America. They regularly attended the American meetings and have established warm relations with many Canadian and American colleagues. The first two meetings of the European Society of Pediatric Radiology, held in Paris in 1962 and 1963, led to successful cooperation among the pediatric radiologists of all Europe and had great influence overseas. To bridge the language barrier, Dr. Lefèbvre agreed—a bitter pill for a Frenchman, and at a time when official directives were quite contrary to this—to make English the sole language of the annual meetings of the society.

Many will recall meeting Jacques Lefèbvre and his charming wife Lucie at the 1974 San Francisco session of the Society for Pediatric Radiology, where he delivered a paper titled "Diverticula of the Bladder in Childhood." Besides his professional achievements, we will always remember him for his economy of movement and word, his tall stature, his wisdom, his humanity, and his forcefulness. He may often have appeared to hide behind a mask, but those who knew him well enjoyed his vibrating friendship and glowing warmth. His habitual smile was never ironic, always full of good will.

Those who did not see Jacques Lefèbvre within his own setting in France or were not able to communicate with him in his own language will never fully appreciate the loss radiology has suffered by the sudden departure of this remarkable man.

H. J. Kaufmann and
E. B. D. Neuhauser

NEWS ITEMS

PEDIATRIC RADIOLOGY

This postgraduate course in pediatric radiology, organized by the Department of Radiology of the Albert Einstein College of Medicine and its affiliated hospitals, will be held May 12–16, 1975. The course is intended for radiologists and pediatricians. A comprehensive review of present day concepts of pediatric radiology will be presented.

The continuing Medical Education Programs at the Albert Einstein College of Medicine have been accredited by the Council on Medical Education of the American Medical Association for a Category 1 Award and are acceptable for credit toward the American Medical Association Physician's Recognition Award.

The Program Chairman is Milton Elkin, M.D., and the Program Co-Chairman is Harold G. Jacobson, M.D.

The place is Robbins Auditorium, Albert Einstein College of Medicine, Eastchester Road and Morris Park Avenue, Bronx, New York.

Accommodations for housing and transportation may be arranged at the Waldorf Astoria Hotel in Manhattan upon notifying intention with reference to reservations. A special rate request card will be held and transportation will be provided between the medical school and this hotel. Registration before April 25th is necessary in order to secure a room at our special rate.

The Guest Faculty includes: Drs. David H. Baker, M.D., Walter E. Berdon, M.D., John Caffey, M.D., M. Paul Capp, M.D., John P. Dorst, M.D., J. Scott Dunbar, M.D., Robert H. Freiberger, M.D., Bertram R. Girdany, M.D., N. Thorne Griscom, M.D., George Kassner, M.D., John A. Kirkpatrick, M.D., William Northway, M.D., M. B. Ozonoff, M.D., Andrew K. Poznanski, M.D., Frederic Silverman, M.D., Melvin Tefft, M.D., Joseph P. Whalen, M.D., and Patricia Winchester, M.D.; in addition to the Local Faculty.

For further information, please write to: Mrs. Claire Delman, Radiology Department, Albert Einstein College of Medicine, Bronx, New York 10461.

POSTGRADUATE COURSE IN MEDICAL THERMOGRAPHY

Physicians are cordially invited to attend a 2 day postgraduate course in "Medical Thermography" at the Johns Hopkins Medical Institutions on Thursday and Friday, June 26 and June 27, 1975.

This program is planned as a comprehensive course on the role of thermography in the diagnosis of various diseases. The history, principles, apparatus and current applications will be discussed. A workshop will provide access to instruments and operating technique. This course will be of value to all physicians in specialty and general practice. The faculty has been carefully selected for its outstanding contribution to the field of thermography.

This program is approved for 15 credit hours in Category 1 towards the Physician's Recognition Award of the A.M.A.

For further information, please contact: Dr. Janet B. Hardy, Director, Continuing Education, The Johns Hopkins Medical Institutions, Turner Auditorium, 720 Rutland Avenue, Baltimore, Maryland 21205.

TEACHING CONFERENCE IN PEDIATRIC RADIOLOGY

This Seminar is sponsored by the Department of Radiology, University of Miami School of Medicine at Jackson Memorial Hospital, October 8–12, 1975.

For further information, please contact: Manuel Viamonte, Jr., M.D., Department of Radiology, University of Miami School of Medicine, Post Office Box 520875, Biscayne Annex, Miami, Florida 33152.

CURRENT CONCEPTS IN PEDIATRIC RADIOLOGY

A 5 day Postgraduate Course on "Cur-

rent Concepts in Pediatric Radiology" will be presented from November 3–7, 1975 at the Pinehurst Hotel in Pinehurst, North Carolina, by the faculty of the Departments of Radiology and Pediatrics, Duke University Medical Center and a distinguished Guest Faculty as follows.

Guest Faculty: David H. Baker, M.D., New York City; Walter E. Berdon, M.D., New York City; M. Paul Capp, M.D., Tucson, Arizona; J. Scott Dunbar, M.D., Vancouver, B. C., Canada; John A. Kirkpatrick, M.D., Boston, Massachusetts; Edward B. Singleton, M.D., Houston, Texas; and Rick I. Suberman, M.D., Chapel Hill, North Carolina.

Duke Faculty: Radiology: Herman Grossman, M.D.; Richard G. Lester, M.D.; Robert McLelland, M.D.; and Michael Oliphant, M.D.; Pediatrics: Samuel L. Katz, M.D., and Catherine Wilfert, M.D.

There will be a systems oriented format covering Cardiopulmonary diseases on Monday, Gastrointestinal diseases on Tuesday, Genitourinary diseases on Wednesday and Musculoskeletal diseases on Thursday, with Friday left for miscellaneous disorders.

This program is open to all physicians having an interest in these subjects and there will be 25 hours of A.M.A. Category 1 accreditation.

The Program Chairman is Richard G. Lester, M.D., Professor and Chairman of Radiology, Duke University Medical Center. Inquiries should be directed to the Program Director: Robert McLelland, M.D., Radiology-Box 3808, Duke University Medical Center, Durham, North Carolina 27710.

OPERATIONAL HEALTH PHYSICS

The Health Physics Society's ninth midyear symposium will be held in Denver, Colorado, February 9–12, 1976, at the Denver Hilton Hotel.

The theme for the meeting is Operational Health Physics with emphasis on ionizing and non-ionizing radiation monitoring, exposure and contamination control, exposure evaluation, instrumentation, waste management and emergency planning and response.

For further information, please contact: Jerome B. Martin, P.O. Box 3229, Boulder, Colorado 80303.

BOOK REVIEW

Pediatric Nuclear Medicine. Edited by A. Everette James, Jr., Sc.M., M.D., Associate Professor of Radiology; Director of Radiological Research, The Johns Hopkins University School of Medicine; Henry N. Wagner, Jr., M.D., Professor of Radiology; Director of Nuclear Medicine; Professor of Medicine, The Johns Hopkins University School of Medicine: and Robert E. Cooke, M.D., Vice Chancellor for Health Sciences; Professor of Pediatrics, University of Wisconsin; formerly, Given Foundation Professor of Pediatrics; Director of the Department of Pediatrics, The Johns Hopkins University School of Medicine. Cloth. Pp. 544, with 378 illustrations. Price, $35.00. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. 19105, 1974.

This book of 14 sections with 42 chapters is truly a work on pediatric nuclear *medicine* rather than on isotope scanning in pediatrics. The reviewer, a diagnostic pediatric radiologist, was alarmed at being assigned the task of review until a check of the 85 authors showed virtually everyone involved in pediatric nuclear medicine was a contributor. So be it.

The book has within it something of value for all physicians caring for children, whether pediatricians, radiologists or surgeons, who can benefit from the application of radioactive isotopes in studying both normal function and pathologic function in children.

A large segment of the book is devoted to the biologic implications of the use of radioactive materials—with the search going on for more disease or organ-specific agents of lower dosage. There is an unfortunate repetition in many of the chapters on choice of agent, sedation, etc. It is hoped that the next edition can condense this without losing the excellent biologic overview of the introductory chapters. Particularly interesting to me were those by Doctors Sanger and Kereiakes on radiologic biology in pediatric nuclear medicine, and the discussion of dosages in nuclear medicine *versus* diagnostic x-ray procedures by Webster, Alpert and Brownell.

For example, the endless ordering of repeat skeletal surveys in children with known neoplasm such as neuroblastoma or retinoblastoma would be better replaced by periodic bone scans with skeletal radiographic study of abnormal areas of the bone scan, assuming an *initial normal* skeletal survey. This would involve an intelligent use of isotopes in their role as a seeker of abnormal function (in lieu of the roentgenogram which seeks abnormal structure). The same would lead to bone scans replacing skeletal surveys in looking for "occult osteomyelitis" in a child with fever of unknown origin.

The various anatomic sections include the nervous system, lungs, heart, gastrointestinal and genitourinary tracts, and skeletal system. The neurologic sections are most redundant. For example, the 4 chapters on the brain could easily be combined, as could the 3 sections on cerebrospinal fluid.

The bone scanning section by Bell, Subramanian, Blair and McAfee is excellent. It frankly discusses the "false" positives and negatives that actually show how the scan reflects bone function (as opposed to bone structure).

The genitourinary sections are troublesome to a diagnostic radiologist. The interest in detecting fine anatomic abnormality (renal scarring, mild calyceal distortion) that *may be* of importance in following infantile vesicoureteral reflux (and intrarenal reflux) is not adequately studied by the usual method of doing renal scanning or isotope cystograms. It is possible with improved technique to separate cortical and medullary function in the kidney. The use of particulate agents in isotope cystograms would show retention of radioactive material within the kidney after a voiding cystogram, and there is excellent evidence for intrarenal reflux. It is odd how reluctant the pediatric and genitourinary world is to use such techniques. Part of the problem is the amount of work demanded from the average nuclear medicine department and the "fear of the unknown" in leaving the "safe" albeit high radiation world of cine cystograms, etc. The genitourinary problem alone cries out for advances and it is hoped that the next edition will include more renal and lower urinary tract isotopic studies.

The cardiac sections show the amount of information that can be gained in the study of congenital heart disease, including quantitation of existing left to right and right to left shunts,

and evaluation of the efficacy of surgical palliative or corrective procedures on such defects.

There is a section on the relation of angiography to pediatric nuclear medicine. It would be valuable for the nuclear medicine department to utilize the angiographic procedure room. It would be most interesting, if there could be injection of the appropriate isotopes through the catheter directly into the organ. Then correlation could be made of the functional vascular anatomy of a mass (such as a malignant liver tumor) in terms of the rate of dispersion of radioactivity from a bolus injected into the tumor, as opposed to the radiographic imaging of the tumor's blood supply. The "early filling of veins" would be quantitated by the isotopic studies. As it is now, most pediatric x-ray departments rely on the scan in tumor patients more for structure (cold spots in the liver) than for function.

Finally, it is difficult to reconcile the radiographic trend to smaller focal spots, and magnification radiographic techniques, axial tomography, etc. with the philosophy of nuclear medicine expressed by Doctor Cooke, a pediatrician and one of the authors, that the "pediatrician must *conceptualize* (italics by the author) abnormality rather than *visualize* it."

This reviewer agrees and disagrees . . . it all depends on what is of interest. This first edition of Pediatric Nuclear Medicine should serve as a stimulus and goal to those of us who have too much relied on visualizing abnormality. It is hoped that a friendly, rather than adversary, relation can characterize the intertwining pediatric radiology and pediatric nuclear medicine. Perhaps this review does more than scan an excellent beginning.

I found the book lavishly illustrated and most interesting. It is well worth purchasing since it clearly will be *the* authority in its field for the foreseeable future. The editors are to be congratulated.

Walter E. Berdon, M.D.

BOOKS RECEIVED

Advances and Technical Standards in Neurosurgery. Edited by H. Krayenbühl, Zürich, J. Brihaye, Bruxelles, F. Loew, Homburg/Saar, V. Logue, London, S. Mingrino, Padova, B. Pertuiset, Paris, L. Symon, London, H. Troupp, Helsinki, and M. G. Yaşargil, Zürich. Cloth, Pp. 210, with many figures. Price, $32.40. Springer-Verlag, New York, 1974.

Radionuclide Scanning in Cyanotic Heart Disease. By Gary F. Gates, M.D., Assistant Research Physician (Nuclear Medicine), Laboratory of Nuclear Medicine and Radiation Biology, University of California at Los Angeles, Los Angeles, Calif.; Director, Pediatric Radiology, Memorial Hospital Medical Center and Earl and Loraine Miller Children's Hospital of Long Beach, Long Beach, Calif. Cloth. Pp. 100, with some figures. Price, $15.00. Charles C Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Ill. 62717, 1974.

Radiology of the Ileocecal Area. Robert N. Berk, M.D., Professor and Chairman, Department of Radiology, University of Texas Southwestern Medical School, Dallas, Texas; and Elliott C. Lasser, M.D., Professor and Chairman, Department of Radiology, University of California, San Diego School of Medicine, San Diego, Calif. Cloth. Pp. 327, with 246 illustrations. Price, $22.00. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. 19105, 1975.

The Accessory Digestive Organs. By Robert E. Wise, M.D., Chairman, Department of Diagnostic Radiology, Lahey Clinic Foundation; Chairman, Department of Radiology, New England Baptist Hospital; Clinical Professor of Radiology, Boston University School of Medicine; and Austin P. O'Keeffe, M.B., B.Ch., Radiologist, Exeter Hospital, Exeter, N. H.; Teaching Associate, Department of Diagnostic Radiology, Lahey Clinic Foundation. Cloth. Pp. 331, with many illustrations. Price, $27.95. Year Book Medical Publishers, 35 East Wacker Drive, Chicago, Ill. 60601, 1975.

Pneumography in Paraventricular and Intraventricular Tumours of the Posterior Fossa. By Anders Möller, Department of Neuroradiology, Karolinska Sjukhuset, Stockholm, Sweden. Acta Radiologica Supplementum 342. Paper. Pp. 145, with some illustrations. Price, Sw. Kr. 60.—. Acta Radiologica, Vasagatan 12, S-111 20 Stockholm, Sweden, 1974.

The Radioactive Patient. Care, Precautions, and Procedures in Diagnosis and Therapy. By Earl Van Roosenbeek, Radiation Safety Officer, Instructor in Physics; and Luis Delclos, M.D., F.A.C.R., Radiotherapist, Professor of Radiotherapy, The University of Texas Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston, Texas. Paper. Pp. 128, with some figures. Price, $10.00. Medical Examination Publishing Company, Inc., 65-36 Fresh Meadow Lane, Flushing, N. Y. 11365, 1975.

Current Concepts in Radiology. Volume two. Edited by E. James Potchen, M.D., Professor, Department of Radiology, The Johns Hopkins Medical Institutions, Baltimore, Md. Cloth. Pp.

328, with some illustrations. Price, $35.00. C. V. Mosby Company, Publishers, 3301 Washington Boulevard, St. Louis, Mo. 63103, 1975.

Fundamentals of Radiation Therapy and Cancer Chemotherapy. By Sidney Lowry, M.D., Professor of Cancer Studies, The Queen's University of Belfast; Formerly, Director of Radiation Therapy, Maine Medical Center, Portland, Maine; Assistant Professor of Therapeutic Radiology, Tufts-New England Medical Center, Boston. Paper. Pp. 198, with some figures. Price, $7.50. Arco Publishing Company, Inc., 219 Park Avenue South, New York, N. Y. 10003, 1975.

The Cell Cycle in Malignancy and Immunity. Proceedings of the Thirteenth Annual Hanford Biology Symposium at Richland, Wash., Oct. 1–3, 1973. Sponsored by Battelle Pacific Northwest Laboratories and U. S. Atomic Energy Commission. James C. Hampton, Chairman. Paper. Pp. 618, with 265 illustrations. CONF-731005. Price, $13.60. National Technical Information Service, U. S. Department of Commerce, Springfield, Va. 22161, 1975.

Predicting Adult Stature for Individuals. By A. F. Roche, H. Wainer, and D. Thissen, Fels Research Institute, Yellow Springs, Ohio and Department of Behavioral Sciences, University of Chicago, Chicago, Ill. Volume 3, in Monographs in Paediatrics. Paper. Pp. 114, with 17 figures. Price, $20.00. Albert J. Phiebig, Inc., U. S. Representative of S. Karger, P. O. Box 352, White Plains, N. Y. 10602, 1975.

SOCIETY PROCEEDINGS

MEETINGS OF RADIOLOGICAL SOCIETIES*

United States of America

American Roentgen Ray Society
Secretary, Dr. James Franklin Martin, 300 S. Hawthorne Rd., Winston-Salem, N. C. 27103. Annual Meeting: Marriott Hotel, Atlanta, Ga., Sept. 30–Oct. 3, 1975.

American Radium Society
Secretary, Richard H. Jesse, Dept. of Surgery, M. D. Anderson Hosp. and Tumor Institute, Houston, Tex. 77025. Annual Meeting: Americana Hotel, San Juan, Puerto Rico, May 4–9, 1975.

Radiological Society of North America
Secretary, Dr. Theodore A. Tristan, Harrisburg, Pennsylvania. Annual Meeting: McCormick Place on the Lake, Chicago, Ill., Nov. 30–Dec. 5, 1975.

American College of Radiology
Executive Director, William C. Stronach, 20 N. Wacker Drive, Chicago, Ill. 60606. Annual meeting: Portland-Hilton Hotel, Portland, Oregon, March 31–April 4, 1975.

Section on Radiology, American Medical Association
Secretary, Dr. Antolin Raventos, Davis, Calif. Annual Meeting: Atlantic City, N. J., June 15–19, 1975.

American Board of Radiology
Secretary, Dr. C. Allen Good. Correspondence should be directed to Kahler East, Rochester, Minn. 55901.

Written Examination will be held in 14 selected sites, June 21, 1975.

Oral examinations will be held: Pittsburgh Hilton, Pittsburgh, Pa., June 2–7, 1975; Statler Hilton, Dallas, Texas, Dec. 8–13, 1975; Marriott Motor Hotel, Chicago, Ill., June 14–19, 1976; Sheraton Biltmore, Atlanta, Ga., Dec. 6–11, 1976.

Applications must be received in the Board Office before Sept. 30 of the year preceding the one in which the candidate wishes to be examined.

Deadline for filing applications for any examination in 1976 is September 30, 1975.

American Board of Nuclear Medicine, Inc. A Conjoint Board of the American Boards of Internal Medicine, Pathology and Radiology and sponsored by the Society of Nuclear Medicine.

Application forms and further information are available from the American Board of Nuclear Medicine, 305 E. 45th St., New York, N. Y. 10017.

American Association of Physicists in Medicine
Secretary, Dr. Robert G. Waggener, Dept. Radiol., Univ. Tex. Health Sciences Center, San Antonio, Tex. 78284. Annual Meeting, Aug. 3–7, 1975.

American Society of Therapeutic Radiologists
Secretary, Dr. Robert W. Edland, 1836 South Ave., La Crosse, Wis., 54601. Annual Meeting: Hyatt Regency Hotel in the Embarcadero Center, San Francisco, Calif., Oct. 8–12, 1975.

American Nuclear Society
Program Chairman, Werner K. Kern, IRD, Space Nuclear Systems, F 309, U. S. Atomic Energy Commission, Washington, D.C. 20545.

American Institute of Ultrasound in Medicine
Secretary, John M. Reid, Ph.D., 556 18th Ave., Seattle, Wash. 98122. Annual Meeting.

American Society of Neuroradiology
Secretary, Dr. David O. Davis, Department of Radiology, 901 Twenty-third St., N.W., Washington, D. C. 20037. Annual Meeting.

Fourteenth International Congress of Radiology
Rio de Janeiro, Brazil, Oct. 23–29, 1977.

International Society of Radiology
Hon. Secretary-Treasurer, Prof. W. A. Fuchs, M.D., Department of Diagnostic Radiology, University Hospital, Inselspital, CH-3010 Bern, Switzerland.

Eleventh Inter-American Congress of Radiology
Counselor for the United States, Dr. Juan A. del Regato, Univ. of South Florida, College of Medicine, Tampa, Fla.
Secretary of Congress, Dr. Alberto Mejia, Apartado Aéreo 53737, Bogotá 2, Colombia. Meeting: Feb. 16–21, 1975.

Inter-American College of Radiology
President, Dr. Miguel Dao y Dao, Apartado Postal 14213, Candelaria, Caracas, Venezuela, S.A.
Secretary of Congress: Dr. Alberto Mejia, Apartado Aéreo 53737, Bogotá 2, Colombia, S.A. Meeting: Bogotá, Colombia, Feb. 16–21, 1975.

Third Congress of the European Association of Radiology
Secretary-General, P.O. Box 14, 79 Lauriston Place, Edinburgh BHI IDB, Scotland, Meeting: June 22–27, 1975.

Second Asian and Oceanian Congress of Radiology
Secretary, Dr. Buenaventura U. V. Angtuaco, Congress Secretariat Headquarters, 2161 Taft Ave., Manila, Philippines. Meeting: Manila, Philippines, Nov. 10–14, 1975.

Alabama Chapter of ACR
Secretary-Treasurer, Dr. Lawrence E. Fetterman, 1720 Springhill Ave., Suite 201, Mobile, Ala. 36604. Meets time and place of Alabama State Medical Association.

Alaska Radiological Society, Chapter ACR
Secretary-Treasurer, Dr. Maurice J. Coyle, 3200 Providence Ave., Anchorage, Alaska 99504.

American Osteopathic College of Radiology
Annual Scientific Meeting: Americana Hotel, Bar Harbor, Fla. Program Administrator: Lawrence J. Jordan, D.O., Suite 21, Ponce American Bldg., 4601 Ponce de Leon Blvd., Coral Gables, Fla. 33146.

American Thermographic Society
Secretary-Treasurer, John Wallace, Ph.D., Dept. Radiol., Thomas Jefferson Univ. Hosp., Philadelphia, Pa. 19107. Annual Meeting.

Arizona Radiological Society, Chapter of ACR
Secretary, Dr. Robert J. Johnson, 1603 N. Tucson Blvd., Tucson 85716. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meeting six months later.

Ark-La-Tex Radiological Society
Secretary, Dr. Erich K. Lang, Confederate Memorial Medical Center, LSU School of Medicine, Shreveport, La. 71101.

Arkansas Chapter of ACR
Secretary-Treasurer, Dr. David H. Newbern, 4301 W. Markham, Little Rock, Ark. 72205. Meets twice annually, the Spring Meeting being in conjunction with and at the place of the State Medical Association.

Association of University Radiologists
Secretary-Treasurer, Dr. Mark M. Mishkin. The Graduate Hosp., Univ. of Pennsylvania, Philadelphia, Pa. 23rd Annual Meeting: San Diego, Calif., May 4–6, 1975.

Atlanta Radiological Society
Secretary-Treasurer, Dr. Marshall J. Cantanzaro, Dept. of Radiol., Northside Hosp., Atlanta, Ga. 30342. Meets on fourth Thursday evenings during the academic year at a

*** Secretaries of societies are requested to send timely information promptly to the Editor.**

time announced in early September of each year, at the Academy of Medicine, Atlanta, Ga., at 8:00 P.M.

Bavarian-American Radiologic Society
Secretary, Maj. Marco J. DiBiase, M.D., Radiology Service, 130 Station Hosp., APO N. Y. 09102. Next Meeting: Berlin, March 14–16, 1975.

Blockley Radiological Society
Secretary-Treasurer, Dr. Joseph H. Rosen, West Park Hospital, 3905 Ford Rd., Philadelphia, Pa. 19131.

Bluegrass Radiological Society
Secretary-Treasurer, Dr. Eugene Slusher, Lexington Clinic, 1221 S. Broadway, Lexington, Ky. 40504. The Society meets once each month during the school year.

Bronx Radiological Society, New York State, Chapter ACR
Secretary-Treasurer, Dr. Leon J. Corbin, 1369 Rosendale Ave., Bronx, N. Y. 10472. Meets 4 times a year.

Brooklyn Radiological Society
Secretary-Treasurer, Dr. Joshua A. Becker, Downstate Medical Clin., 450 Clarkson Ave., Brooklyn, N. Y. 11203. Meets first Thursday of each month, October through June.

Buffalo Radiological Society
Secretary, Dr. George J. Alker, Jr., E. J. Meyer Mem. Hosp., Buffalo, N. Y. 14215. Meets second Monday evening each month, October to May inclusive, at University Club.

California Radiation Therapy Association
Secretary-Treasurer, Dr. James R. Eltringham, Stanford Medical Center, Stanford, Calif. 94304. Meets semiannually in San Francisco and Los Angeles.

California Radiological Society, California Chapter of ACR
Secretary-Treasurer, Dr. John L. Gwinn, 4650 Sunset Blvd., Los Angeles, Calif. 90027.

Catawba Valley Radiological Society
Secretary, Dr. Walter Joe Jacumin, P.O. Box 265, Rutherford College, N. C. 28671. Meets the last Thursday of every month, Holiday Inn, Morganton, N. C. at 7:30 P.M.

Central New York Radiological Society
Secretary-Treasurer, Dr. Alfred Brettner, Auburn Mem. Hosp., Auburn, N. Y. 13021. Meets first Monday each month October through May.

Central Ohio Radiological Society
Secretary-Treasurer, Dr. Daniel E. Lewis, Grant Hosp., Columbus, Ohio 43215. Meets second Thursday in October, November, January, and March 15, and May 19 at Fort Hayes Hotel, Columbus, Ohio.

Central Texas Radiology Society
Secretary-Treasurer, Dr. John M. Stoebner, Scott and White Clinic, Temple, Tex. 76501. Meets the fourth Monday of each month at Ponderosa Hotel, Temple, Tex. at 7:00 P.M.

Chicago Radiological Society, Division of the Illinois Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Harold J. Lasky, 55 E. Washington St., Suite 1735, Chicago, Ill. 60602. Meets third Thursday of each month, October to April, except December, at the Bismark Hotel, Chicago, Ill.

Cleveland Radiological Society
Secretary-Treasurer, Dr. Charles M. Greenwald, 7007 Powers Blvd., X-Ray Dept., Parma, Ohio 44129. Meetings at 7:00 P.M. on fourth Monday of October, November, January, February, March and fifth Monday of April.

Colorado Radiological Society, Chapter of ACR
Secretary, Dr. Jerome D. Sutherland, 3705 E. Colfax Ave., Denver, Colo. 80206. Meets third Friday of each month at Denver Athletic Club from September through May.

Connecticut Valley Radiologic Society
Secretary, Dr. Gerald N. LaPierre, 759 Chestnut St., Springfield, Mass. 01107. Meets in April and October.

Dallas-Fort Worth Radiological Society
Secretary-Treasurer, Dr. Robert R. Burns, 1400 Stemmons Ave., Dallas, Tex. 75208. Meets the 3rd Monday of every month at 6:30 P.M., at the Airport Hotel, Arlington, Tex.

Delaware Chapter of ACR
Secretary, Dr. Seymour R. Kaplan, Kent Gen. Hosp., Dover, Del. 19901.

East Bay Radiological Society
Secretary-Treasurer, Dr. Robert L. Stein, 43 Dormidera Ave., Piedmont, Calif. 94611. Meets first Thursday each month, Oct. through May, at University Club, Oakland, Calif.

East Tennessee Radiological Society
Secretary-Treasurer, Dr. George H. Wood, 205 Medical Arts Bldg., Knoxville, Tenn. 37902. Meets in January and September.

Florida Radiological Society, Chapter of ACR
Secretary. Dr. Paul J. Popovich, 1350 S. Hickory St., Melbourne, Fla. 32901. Meets twice annually, in the spring with the Annual State Society Meeting and in the fall.

Florida West Coast Radiological Society
Secretary-Treasurer, Dr. Herbert Johnson, Davis Blvd., Tampa, Fla. 33606. Meets on 4th Thursday of the months January, March, May, October, and November.

Georgia Radiological Society, Chapter of ACR
Secretary, Dr. E. P. Rasmussen, Piedmont Prof. Bldg., 35 Collier Rd., N.W., Atlanta, Ga. 30309.

Greater Cincinnati Radiological Society
Secretary-Treasurer, Dr. Owen L. Brown, 2421 Auburn Ave., Cincinnati, Ohio 45219.

Greater Kansas City Radiological Society
President-Secretary, Dr. Keith W. Gallehugh, Bethany Med. Center, Kansas City, Kans. Meets 5 times a year.

Greater Louisville Radiological Society
Secretary-Treasurer, Dr. L. D. LeNeave, 315 E. Broadway, Louisville, Ky. 40202. Meets monthly.

Greater Miami Radiological Society
Secretary-Treasurer, Dr. Robert F. Conti, Holy Cross Hosp., Fort Lauderdale, Fla. 33308. Meets monthly, third Wednesday at 8:00 P.M. at various member hospitals, Miami, Fla.

Greater St. Louis Society of Radiologists
Secretary-Treasurer, Dr. Donald Callahan, Northland Med. Bldg., Jennings, Mo. 63136.

Hawaii Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Sidney B. W. Wong, Straub Clinic and Hosp., Honolulu, Hawaii 96813. Meets third Monday of each month at 7:30 P.M.

Health Physics Society
Secretary, Russell F. Cowing, P.O. Box 156, E. Weymouth, Mass. 02189. Annual Meeting.

Houston Radiological Society
Secretary, Dr. Neill B. Longley, 6436 Fannin, Suite 601, Houston, Tex. 77025. Meets fourth Monday of each month, except June, July, August and December, at 6:00 P.M., at 103 Jesse H. Jones Library Building, Texas Medical Center, Houston, Tex. 77025.

Idaho State Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. John H. Truksa, 1605 Park Ave., Nampa, Id. 83651. Meets in the spring and fall.

Illinois Radiological Society, Inc., Chapter of ACR
Secretary, Dr. Robert D. Dooley, Hinsdale Med. Center, Hinsdale, Ill. 60521. Meets in the spring and fall.

Indiana Roentgen Society, Inc., Chapter of ACR
Secretary, Dr. John A. Knote, 716 Carrolton Blvd., West Lafayette, Ind. 47906.

Iowa Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. John Huston, Jr., 1948 First Ave., N.E., Cedar Rapids, Iowa 52402. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific session is held in the autumn.

Kansas Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Ralph H. Baehr, 310 Medical Arts Bldg., Topeka, Kan. 66604. Meets in spring with State Medical Society and in winter on call.

KENTUCKY CHAPTER OF ACR
Secretary-Treasurer, Dr. Bernard Sams, St. Joseph Infirmary, 735 Eastern Parkway, Louisvlle, Ky. 40217. Meets in April and September.

KINGS COUNTY RADIOLOGICAL SOCIETY
Secretary, Dr. Sidney Hendler, 1880 Ocean Ave., Brooklyn 30, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

KNOXVILLE RADIOLOGICAL SOCIETY
Secretary, Dr. Clifford L. Walton, Blount Professional Bldg., Knoxville 20, Tenn. Meetings are held the third Monday of every other month at the University of Tennessee Memorial Research Center and Hospital.

LONG ISLAND RADIOLOGICAL SOCIETY
Secretary, Dr. Bruce Saxe, 1200 Stewart Ave., Garden City, N. Y. 11533. Meets monthly.

LOS ANGELES RADIOLOGICAL SOCIETY
Secretary, Dr. Isaac Sanders, 1429 Valley View Rd. 13, Glendale, Calif. 91202. Meets second Wednesday of month in September, November, January, April and June at Los Angeles County Medical Association Building, Los Angeles, Calif. Midwinter Radiological Conference. Century Plaza Hotel, Los Angeles, Calif.

LOUISIANA RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary-Treasurer, Dr. Roger H. Tutton, 1514 Jefferson Hwy., New Orleans, La. 70121.

LOUISIANA-TEXAS GULF COAST RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Arnold G. Manske, P.O. Box 3008, Port Arthur, Tex. 71670.

MAINE RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary-Treasurer, Dr. Richard W. Taylor, Radiology Department, St. Mary's General Hospital, Lewiston, Maine 04240. Meets in June, September, December and April.

MARYLAND RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary, Dr. David S. O'Brien, Anne Arundel Hosp., Annapolis, Md. 21401.

MASSACHUSETTS RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary, Dr. Joseph T. Ferrucci, Jr., Massachusetts Gen. Hosp., Boston, Mass. 02114.

MEMPHIS ROENTGEN SOCIETY
Secretary-Treasurer, Dr. Thomas P. Coburn, The University of Tennessee College of Medicine, Department of Radiology, Walter C. Chandler Bldg., 865 Jefferson Ave., Memphis, Tenn. 38163. Meets first Monday Oct. through May at the University Club.

MIAMI VALLEY RADIOLOGICAL SOCIETY
Secretary, Dr. Bert Must, I.B.M. Bldg., Dayton, Ohio. Meets third Thursday of fall, winter and spring months at 7:30 P.M. at Miami Valley Hospital, Dayton, Ohio.

MICHIGAN RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary-Treasurer, Dr. Francis P. Shea, Harper Hospital, 3825 Brush St., Detroit, Mich. 48201. Meets monthly, first Thursday, October through May, at David Whitney House, 1010 Antietam, at 6:30 P.M.

MICHIGAN SOCIETY OF THERAPEUTIC RADIOLOGISTS
Secretary-Treasurer, Dr. Delmar Mahrt, William Beaumont Hosp., Detroit, Mich. 48072. Meets bi-monthly during the academic year.

MID-HUDSON RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. William D. Stiehm, 37 Flower Hill Rd., Poughkeepsie, N. Y. 12603. Meets 7:00 P.M., first Wednesday of each month, September to May.

MILWAUKEE ROENTGEN RAY SOCIETY
Secretary-Treasurer, Dr. Thomas C. Lipscomb, 1004 North Tenth St., Milwaukee, Wis. 53233. Meets monthly on fourth Monday, October through May, at University Club.

MINNESOTA RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary-Treasurer, Dr. Marvin E. Goldberg, Box 292, Mayo Memorial Health Sciences Center, Minneapolis, Minn. 55455.

MISSISSIPPI STATE RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary-Treasurer, Dr. Edward L. Gieger, 969 Lakeland Dr., Jackson, Miss. 39216. Meets third Thursday, excluding summer months, at the Primos Northgate Rest., Jackson at 6:30 P.M.

MISSOURI RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary-Treasurer, Dr. Ronald G. Evens, Mallinckrodt Institute of Radiology, 510 S. Kingshighway, St. Louis, Mo. 63110.

MONTANA RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary, Dr. C. H. Agnew, Room 102, Doctors Bldg., Billings, Mont. 59101.

NEBRASKA CHAPTER OF ACR
Secretary-Treasurer, Dr. Robert Bodmer, Suite 622 Doctors Bdg., Omaha, Neb. 68131. Meets the third Wednesday of the month, Oct. through March, at the Clarkson Hosp., Omaha, Neb. and the fourth Friday of April at the Lincoln Country Club, Lincoln, Neb.

NEVADA RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary, Dr. Charles F. Veverka, Carson Tahoe Hosp., Carson City, Nev. 89701.

N.E. SOCIETY FOR RADIATION ONCOLOGY
Secretary, Dr. C. C. Wang, Mass. Gen. Hosp., Boston, Mass. 02114.

NEW ENGLAND ROENTGEN RAY SOCIETY
Secretary, Dr. Melvin E. Clouse, 185 Pilgrim Rd., Boston, Mass. 02115. Meets the third Friday of each month, October through April, excluding December, at The Longwood Towers, 20 Chapel Street, Brookline, Mass. at 3:00 P.M. Annual Meeting: May 16, 1975.

NEW HAMPSHIRE ROENTGEN RAY SOCIETY, CHAPTER OF ACR
Secretary-Treasurer, Dr. Edward P. Kane, Claremont Gen. Hosp., Claremont, N. H. 03743. Meets four to six times yearly.

NEW MEXICO SOCIETY OF RADIOLOGISTS, CHAPTER OF ACR
Secretary, Dr. W. M. Jordan, 1100 Central Ave. S.E., Albuquerque, N. M. 87106. Four meetings annually, three held in Albuquerque, N. M., and one held at time and place of New Mexico State Medical Society annual meeting.

NEW ORLEANS RADIOLOGICAL SOCIETY, INC.
Secretary-Treasurer, Dr. Jimmy L. Mains, P.O. Box 446, Gretna, La. 70053. Meets bimonthly at local restaurants selected by the President. Spring Conference.

NEW YORK ROENTGEN SOCIETY
Secretary-Treasurer, Dr. Thomas C. Beneventano, 110 East 210th St., Bronx, N. Y. 10467. Meets monthly on the 3rd Monday at the New York Academy of Medicine at 4:30 P.M. Annual Spring Conference, Waldorf-Astoria Hotel, New York, N. Y., April 24–26, 1975. A.M.A. Cat. I credit. Further information may be obtained from Dr. Albert A. Dunn, Roosevelt Hosp., New York, N. Y. 10019.

NEW YORK STATE CHAPTER OF ACR
Secretary-Treasurer, Dr. Albert F. Keegan, 6 Secor Dr., Port Wash., N. Y. 11050.

NORTH AMERICAN SOCIETY OF CARDIAC RADIOLOGY
Secretary-Treasurer, Dr. Erik Carlson, Univ. Calif., San Francisco, Calif. 94143.

NORTH CAROLINA CHAPTER OF ACR
Secretary-Treasurer, Dr. Ernest B. Spangler, Wesley Long Hosp., Greensboro, N. C. 27402. Meets twice a year. The Spring Meeting is held at the time of the meeting of the North Carolina Medical Society. The Fall Meeting is held in November at the Mid Pines Club, Southern Pines, N. C.

NORTH DAKOTA RADIOLOGICAL SOCIETY, CHAPTER OF ACR
Secretary, Dr. Pablo Ramos, Box 1618, Bismarck, N. D. 58501. Meets at time of State Medical Association meeting. Other meetings arranged on call of the President.

NORTH FLORIDA RADIOLOGICAL SOCIETY
Secretary, Dr. David F. Bew, University Hospital of

Jacksonville, 655 W. Eighth Street, P.O. Box 2751, Jacksonville, Fla. 32203. Meets quarterly in March, June, September and December.

Northeastern Oklahoma Radiological Society
Secretary-Treasurer, Dr. Theodore J. Brickner, Jr., 5919 S. Gary Place, Tulsa, Okla. 74110.

Northeastern New York Radiological Society
Secretary, Dr. Donald R. Morton, Dept. of Radiology, St. Clare's Hosp., Schenectady, N. Y. 12304. Meets in Albany area on third Wednesday of October, November, March, April, and May.

Northern California Radiation Therapy Association
Secretary-Treasurer, Dr. James R. Eltringham, Stanford Medical Center, Stanford, Calif. 94304. Meets quarterly.

Northern California Radiological Society
Secretary, Dr. Mark D. Reiss, 5301 F Street, Sacramento, Calif. 95819. Meets on the fourth Monday of Sept., Nov., Jan., March and May at the Mansion Inn, Sacramento, Calif.

Northwestern New York Radiological Society
Secretary, Dr. Barbara E. Chick, Glens Falls Hospital, Glens Falls, N. Y. 12801.

Northwestern Ohio Radiological Society
Secretary, Dr. Doug Ki Cho, 2730 Navarre Ave., Oregon (Toledo), Ohio 43616. Meets 3rd Wednesday from September to May.

Ohio State Radiological Society, Chapter of ACR
Secretary, Dr. Tearle L. Meyer, 175 S. Merkle Rd., Columbus, Ohio 43215.

Oklahoma State Radiological Society, Chapter of ACR
Secretary, Dr. George H. Ladd, 4616 Denison, Muskogee, Okla. 74401. Meets in January, May and October.

Orange County Radiological Society
Secretary, Dr. William E. Danko, 2601 E. Chapman, Orange, Calif. 92667. Meets on fourth Tuesday of the month, excluding June, July, August, and December, at Orange County Medical Association Bldg., Orange, Calif.

Oregon State Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Robert E. Craven, P.O. Box 12542, Portland, Ore. 97212. Meets on second Wednesday of month, October through April, at the University Club, Portland, Ore.

Orleans Parish Radiological Society
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans, La. 70113. Meets second Tuesday of each month.

Pacific Northwest Radiological Society
Secretary-Treasurer, Dr. Betty J. Wood, Dept. of Radiol., Vancouver General Hosp., Vancouver 9, B. C., Canada. Annual Meeting.

Pennsylvania Radiological Society, Chapter of ACR
Secretary, Dr. Robert B. Funch, Germantown Hosp., Philadelphia, Pa. 19144.

Philadelphia Roentgen Ray Society
Secretary, Dr. Marvin E. Haskin, 230 N. Broad St., Philadelphia, Pa. 19102. Meets first Thursday of each month at 5 P.M., from October to May in Thompson Hall, College of Physicians.

Pittsburgh Roentgen Society
Secretary, Dr. Klaus M. Bron, Presbyterian-Univ. Hosp., Pittsburgh 15213. Meets second Wednesday of month, September through May, at the Pittsburgh Athletic Association.

Radiation Research Society
Executive Secretary, Richard J. Burk, Jr., 4211 39th St., N.W., Washington, D. C. 20016. Annual Meeting.

Radiological Society of Connecticut, Inc., Chapter of ACR
Secretary-Treasurer, Dr. Mehdi S. Eslami, 1389 W. Main St., Waterbury, Conn. 06708.

Radiological Society of Greater Cincinnati
Secretary-Treasurer, Dr. Alvin Nathan, c/o Academy of Medicine, 320 Broadway, Cincinnati, Ohio 45202. Meets first Monday of each month at Cincinnati Academy of Medicine.

Radiological Society of New Jersey, Chapter of ACR
Secretary, Dr. Sidney Ketyer, St. Elizabeth Hosp., 225 Williamson St., Elizabeth, N. J. 07207. Meets in Atlantic City at time of State Medical Society meeting and in October or November in Newark, N. J.

Radiological Society of Rhode Island, Chapter of ACR
Secretary-Treasurer, Dr. Daniel J. Alves, Rhode Island Hosp., Providence, R. I. 02902.

Radiological Society of Southern California
Secretary-Treasurer, Dr. A. Franklin Turner, LAC-USC Medical Center, Room 3418, 1200 North State St., Los Angeles, Calif. 90033. Meets three times a year, usually October, February and May.

Radiological Society of the State of New York
Secretary-Treasurer, Dr. John W. Colgan, 273 Hollywood Ave., Rochester, N. Y. 14618.

Redwood Empire Radiological Society
Secretary, Dr. Charles E. Carter, 121 Sotoyome St., Santa Rosa, Calif. 95405. Meets second Monday every other month.

Richmond County Radiological Society
Secretary, Dr. Donald P. King, 218 Gun Club Rd., Richmond, Va. 23221. Meets first Thursday of each month at various hospitals.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary-Treasurer, Dr. Robert J. Bruneau, 1441 East Ave., Rochester, N. Y. 14610. Quarterly meetings on the call of the President, at the Rochester Academy of Medicine.

Rocky Mountain Radiological Society
Secretary-Treasurer, Dr. Lorenz R. Wurtzebach, 4200 E. Ninth Ave., Denver, Colo. 80220. Annual meeting: Brown Palace Hotel, Denver, Colo., Aug. 21–23, 1975.

San Antonio-Civilian Military Radiological Society
Secretary, Dr. James R. Stewart, Oak Hills Medical Ctr., San Antonio, Tex. 78209. Meets third Wednesday of each month at Fort Sam Houston Officers Club at 6:30 P.M.

San Diego Radiological Society
President, Dr. Stanley G. Seat, 476 Prospect St., La Jolla, Calif. 92037. Meets the first Wednesday of each month at the University Club.

San Francisco Radiological Society
Secretary-Treasurer, Dr. Charles A. Gooding, Univ. of Calif. Med. Ctr., San Francisco, Calif. 94122.

Section on Radiology, California Medical Association
Secretary, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

Section on Radiology, Medical Society of the District of Columbia
Secretary-Treasurer, Dr. Albert M. Zelna, 21 Masters St., Potomac, Md. 20854. Meets at Medical Society Library, third Wednesday of January, March, May and October at 8:00 P.M.

Section on Radiology, National Medical Association
Secretary, Dr. Ruby Brooks, Dept. Radiol., Veterans Adm. Hosp., P.O. Box 511, Tuskogee, Ala. 36083. Annual Meeting.

Section on Radiology, Southern Medical Association
Secretary, Dr. Mario A. Calonje, 1514 Jefferson Highway, New Orleans, La. 70121. Annual Meeting.

Section on Radiology, Texas Medical Association
Secretary, Dr. George F. Crawford, St. Elizabeth Hospital, Beaumont, Tex. Meets annually with the Texas Medical Association.

Shreveport Radiological Club
Secretary, Dr. W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday at 7:30 P.M., September to May inclusive.

Society for Pediatric Radiology
Secretary-Treasurer, Dr. John P. Dorst, 601 N. Broadway, Baltimore, Md. 21205. Annual meeting: Marriott Hotel, Atlanta, Ga., Sept. 28–29, 1975.

Society of Gastro-intestinal Radiologists
Secretary-Treasurer, Dr. John R. Amberg, University Hospital, 225 W. Dickinson St., San Diego, Calif. 92103.

Society of Nuclear Medicine
Secretary, Dr. E. James Potchen, Edward Mallinckrodt Institute of Radiology, 660 S. Euclid Ave., St. Louis, Mo. 63110. *Administrative Officer*, Mrs. Margaret Glos, 211 E. 43rd St., New York, N. Y. 10017. Annual Meeting.

South Bay Radiological Society
Secretary, Dr. Robert Mindalzun, Valley Radiologists, Inc., 100 O'Connor Dr., San Jose, Calif. 95128. Meets the 2nd Monday of each month at the Santa Clara County Medical Society Bldg., 700 Empey Way, San Jose, Calif.

South Carolina Radiological Society, Chapter of ACR
Secretary, Dr. George W. Brunson, 1406 Gregg St., Columbia, S. C. Annual meeting (primarily business) in conjunction with the South Carolina Medical Association meeting in May. Annual fall scientific meeting at time and place designated by the president.

South Coast Radiological Society Chapter of ACR
Secretary-Treasurer, Dr. Richard T. Love, Santa Barbara Med. Clin., 215 Pesetas Lane, Santa Barbara, Calif. 93110. Meets fourth Tuesday of alternate months, Sept., Nov., Jan., March and May.

South Dakota Radiological Society, Chapter of ACR
Secretary, Dr. M. F. Petereit, 2416 S. Phillips, Sioux Falls, S. D. 57105. Meets in spring with State Medical Society and in fall.

Southern California Radiation Therapy Society
Secretary-Treasurer, Dr. Duane J. Gillum, 250 W. Pueblo St., Santa Barbara, Calif. 93105. Meets quarterly.

Southern Radiological Conference
Secretary-Treasurer, Dr. J. W. Maxwell, P.O. Box 2144 Mobile Ala. 36601. Annual Meeting: Grand Hotel, Point Clear, Ala., Jan. 31–Feb. 2, 1976.

Tennessee Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Charles W. Kimsey, 111 Whitehall Bldg., 960 E. Third St., Chattanooga, Tenn. 37403. Meets annually at the time and place of the Tennessee State Medical Association meeting.

Texas State Radiological Society, Chapter of ACR
Secretary, Dr. Francis E. O'Neill, 1128 Nix Prof. Bdg., San Antonio, Tex. 78205.

The Fleischner Society
Secretary, Dr. E. Robert Heitzman, State University o New York Upstate Medical Center, Syracuse, N. Y. 13210. Annual Meeting: St. Francis Hotel, San Francisco, Calif., May 28–31, 1975.

Tri-State Radiological Society
Secretary, Dr. Alfred Lessure, Welborne Hosp., Evansville, Ind. 47714. Meets bimonthly on the third Wednesday at Arco Hospitals.

Upper Peninsula Radiological Society
Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

Utah State Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Patrick D. Lester, Dept. Radiol., University of Utah Medical Center, Salt Lake City, Utah 84112. Meets quarterly at Holy Cross Hospital.

Vermont Radiological Society, Chapter of ACR
Secretary, Dr. J. Lorimer Holm, R.R. #3, Barre, Vt. 05641.

Virginia Chapter of ACR
Secretary-Treasurer, Dr. Charles P. Winkler, 3500 Kensington Ave., Suite 2-A, Richmond, Va. 23221.

Washington, D. C., Chapter of ACR
Secretary-Treasurer, Dr. Robert M. Allen, 9312 Convento Terr., Fairfax, Va. 22030.

Washington State Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Donald J. Hesch, 3216 N.E. 45th Place, Seattle, Wash. 98105.

West Virginia Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. Andrew W. Goodwin, II, 200 Med. Arts Bldg., Charleston, W. Va. 25301. Meets concurrently with annual meeting of West Virginia State Medical Society, other meetings arranged by program committee.

Westchester County Radiological Society
Secretary, Dr. James O. Richardson, Jr., 280 Mamaronek Ave., White Plains, N. Y. 10605. Meets on second Tuesday of October, December, February and May.

Wisconsin Radiological Society, Chapter of ACR
Secretary-Treasurer, Dr. June Unger, Wood VA Hosp., Wood, Wis. 53193. Meets twice a year, May and September.

Wisconsin Society of Therapeutic Radiologists
Secretary, Dr. Alvin Greenberg, Radiother. Ctr., Univ. Hospitals, Madison, Wis. 53706. Meets quarterly.

Wyoming Radiological Society, Chapter of ACR
Secretary, Dr. Ross J. Collie, Box 96, Lander, Wyo. 82520. Meets in fall with State Medical Society and in spring on call of President.

Mexico, Puerto Rico and Central America

Asociación Costarricense de Radiología
Secretary, Dr. Rafael Umaña-Umaña, Apartado 8-5340, San José, Costa Rica.

Asociacón de Radiólogos de Centro America y Panamá. Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá
Secretary-General, Dr. Francisco Miranbell Solis, Apartado 3352, San José, Costa Rica, Central America. Meets annually in a rotating manner in the six countries.

Asociación Puertorriqueña de Radiología
Secretary, Dr. R. B. Díaz Bonnet, Suite 504, Professional Bldg., Santurce, Puerto Rico.

Sociedad de Radiología de Salvador
Secretary, Dr. Carlos Meijia, 5a Av. Nte. No. 434, San Salvador, Rep. El Salvador.

Sociedad de Radiología de Guatemala
Secretary, Dr. Carlos E. Escobar, 9², Calle A 0–05, Zona 1, Guatemala

Sociedad Mexicana de Radiología, A.C.
Coahuila No. 35, México 7, D.F., México.
Secretary-General, Dr. Jorge Cano Coquí. Meets first Monday of each month.

Sociedad Radiológica Panameña
Secretary, Dr. L. Arrieta Sánchez, Apartado No. 6323, Panamá, R. de P. Meets monthly in a department of radiology of a local hospital chosen at preceding meeting.

Sociedad Radiológica de Puerto Rico
Secretary, Dr. Heriberto Pagán Sáez, Box 9387, Santurce, Puerto Rico. Meets second Thursday of each month at 8:00 P.M. at the Puerto Rico Medical Association Bldg. in San Juan.

British Commonwealth of Nations

Association of Radiologists of the Province of Quebec
121 Boul. Taschereau, Greenfield Park, P. Q., Canada. Meets four times a year.

British Institute of Radiology
Honorary Secretaries, D. H. Traspnell, M. Cohen, 32 Welbeck St., London, W1M/7PG, England.

Canadian Association of Physicists, Division of Medical and Biological Physics
Honorary Secretary-Treasurer, Dr. R. G. Baker, Ontario Cancer Foundation, Ottawa Civic Clinic, 1053 Carling Ave., Ottawa 3, Ont., Canada.

Canadian Association of Radiologists
Honorary Secretary, Dr. Ross O. Hill, Suite 806, 1440 St. Catherine St. West, Montreal 107, Que., Canada. Thirty-eighth Annual Meeting: Toronto, Ont., May 11–16, 1975.

Edmonton and District Radiological Society
Secretary, Dr. L. A. Koller, Suite 360, Professional Bldg., 10830 Jasper Ave., Edmonton 15, Alberta, Canada.

Meets third Thursday of each month October to May, except December, at various Edmonton Hospitals.

Faculty of Radiologists
Honorary Secretary, P. D. Thomson, 28 Portland Pl., London, W1N 4DE.

Montreal Radiological Study Club
Secretary, Dr. W. Paul Butt, Montreal General Hospital, Montreal, Que., Canada. Meets first Tuesday evening, October to April.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets third Friday each month at 8:15 P.M. at the Royal Society of Medicine, 1 Wimpole St., London, W. 1 M8AE, 1 England.

Société Canadienne-Française de Radiologie
Secretary-General, Dr. Hubert Sasseville, Verdun Hospital, Montréal, P. Q., Canada. Meets every third Tuesday from October to April.

The Hospital Physicists' Association
Honorary Secretary, J. B. Massey, B.Sc., Christie Hosp. and Holt Radium Institute, Physics Department, Withington, Manchester M20 9BX, England.

Toronto Radiological Society
Secretary, Dr. George Wortzman, Toronto General Hosp., Toronto 12, Ont., Canada. Meets second Monday of each month, September through May.

The Royal Australasian College of Radiologists
Honorary Secretary, Dr. T. P. Loneragan, 45 Macquarie St., Sydney, N.S.W. 2000, Australia.

South America

Colégio Brasileiro de Radiologia
Secretary-General, Dr. Lauro de Abreu Coutinho, Caixa Postal 5984, São Paulo, Brazil.

Federación Argentina de Sociedades de Radiología
Branches of the Federation are: Sociedad de Radiólogos de la Provincia de Córdoba; Sociedad Argentina de Radiología; Asociación Argentina de Radiología; Sociedad de Radiología, Radioterapéutica y Medicina Nuclear de Rosario; Sociedad de Radiología y Medicina Nuclear del Centro y Sudeste de la Provincia de Buenos Aires (Mar del Plata); Sociedad Salteña de Radiología y Medicina Nuclear; Sociedad de Radiología de Tucumán; Sociedad de Radiologia del Nordeste Argentino; Sociedad de Radiología de La Plata; and Sociedad de Radiología de San Juan.
Secretary-General-Treasurer, Dr. Roberto Habichayn, Av. Colón 637, Córdoba, Argentina.
Congress will be organized by Sociedad de Radiología, Radioterapéutica y Medicina Nuclear de Rosario in 1975.

Sociedad Argentina de Radiología
Secretary-General, Dr. Tomás J. Gutiérrez F, Santa Fé 1171, Buenos Aires, Argentina. Meets first Wednesday evening, April through December.

Sociedad Boliviana de Radiología
Secretary, Dr. Javier Prada Méndez, Casilla 1182, La Paz, Bolivia. Meets monthly. General assembly once every two years.

Sociedade Brasileira de Radiologia
Secretary, Dr. Armando Rocha Amoédo, Caixa Postal 1532, Rio de Janeiro, Brazil. General Assembly meets every two years in December.

Sociedade Brasileira de Radioterapia
Luiz Antonio, 644, São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Chilena de Radiología
Secretary, Dr. Manuel Neira, Casilla 13426, Santiago, Chile. Meets first Friday of each month at Av. Santa María 1810 at 7:00 P.M.

Sociedad Colombiana de Radiología
Secretary-General, Dr. Gustavo Sánchez Sánchez, Bogotá, Colombia. Meets last Thursday of each month.

Sociedad Ecuatoriana de Radiología
Secretary, Dr. Luis Blum, Casilla 3712, Guayaquil, Ecuador.

Sociedad Paraguaya de Radiología
Secretary, Dr. Hugo Volpe Rios, 15 de Agosto 322, Asunción, Paraguay.

Sociedad Peruana de Radiología
Secretary-General, Dra. Ladis Delpino, Av. General Santa Cruz No. 315, Miraflores, Lima, Perú, Casilla Correo, 2306, Lima, Perú. Meets monthly except during January, February, and March.

Sociedad de Radiología del Atlantico
Secretary, Dr. Raul Fernandez, Calle 40 #41-110, Baranquilla, Colombia. Society meets monthly at the Instituto de Radiología.

Sociedad de Radiología del Nordeste Argentino
Secretary-General, Dr. Francisco J. Velar, Catamarca 561, Corrientes, Argentina.

Sociedad de Radiología de La Plata
Secretary, Dr. Hiram D. Haurigot, Calle 50 No. 374, La Plata, Argentina.

Sociedad de Radiología, Cancerología y Física Médica del Uruguay
Secretary-General, Dr. Manuel Gonzáles Maseda, Av. Agraciada 1464, piso 13, Montevideo, Uruguay.

Sociedade de Radiología de Pernambuco
Secretary, Dr. Manoel Medeiros Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife, Caixa Postal 505, Pernambuco, Brazil.

Sociedad de Roentgenología y Medicina Nuclear de la Provincia de Córdoba
Secretary-General, Dr. Lucas C. Di Rienzo, Ave. Grl. Paz. 151, Córdoba, Argentina.

Sociedad de Radiología, Radioterapéutica y Medicina Nuclear de Rosario
Secretary-General, Dr. Federico Frágola, Santa Fe 1798, Rosario, Argentina.

Sociedad Salteña de Radiología y Medicina Nuclear
Treasurer, Dr. Julio Luis Baldi, Av. Sarmiento 536, Salta, Argentina.

Sociedad Venezolana de Radiología y Medicina Nuclear
Secretary-General, Dr. Salvador Itriago Borgas, Apartado Postal 9213, Candelaria, Caracas, Venezuela. Meets monthly, third Friday at Colegio Médico del Distrito Federal, Caracas.

Continental Europe

Österreichische Röntgen-Gesellschaft
Secretary, Dr. Ernst Kotcher, Wiener Allgemeine Poliklinik Mariannengasse 10, A-1090 Wien, Austria. Meets second Tuesday of each month in Allgemeine Poliklinik.

Société Royale Belge de Radiologie
General Secretary, Dr. Joseph Baeyens, Alost, Belgium. Meets in February, March, May, June, September, October, November and December.

Société Européenne de Radiologie Pédiatrique
Secretary, Dr. J. Corbaton, Clinica Infantil "La Paz," Av. Generalissimo, 117 Madrid 34, Spain. Annual Meeting: Madrid, Apr. 24–26, 1975.
Permanent Secretary, Clément Fauré, Hôpital des Enfants Malades, 149, rue de Sèvres, 75 730, Paris Cadet 15, France.

Société Française de Radiologie Médicale, Médecine Nucléaire et Électrologie, and its branches: Société du Sud-Ouest, du Littoral méditerranéen, du Centre et Lyonnais, du Nord, de l'Ouest, de l'Est, du Massif Central, d'Outre-Mer et d'Étranger.
Parent Society meets third Monday of each month, except during July, August and September, rue de Seine 12, Paris, France.
Secretary-General, Dr. Ch. Proux, 9 rue Daru, Paris 75008, France.

Société Française de Neuroradiologie
Secretary-General, Professeur agr. R. Djindjian 16, rue de l'Université 75, Paris 7e, France. Annual meeting.

Československá Radiologická Společnost
Secretary, Associate Professor Jaromír Kolář, M.D., Sc.D., Radiological Clinic, Praha 2, U nemocnice 2, Czechoslovakia. Meets monthly except during July, August and September. Annual general meeting.

Deutsche Röntgengesellschaft
President, Professor Dr. med. Walter Frommhold, Director of Medizinisches Strahleninstitut der Universität Tübingen, Röntgenweg 11, 7400 Tübingen, Germany.

Faculty of Radiologists of the Royal College of Surgeons in Ireland
Honor. Secretary, Max. J. Ryan, St. Stephen's Green, Dublin 2. Annual Meeting, Oct. 25 and 26, 1974.

Società Italiana di Radiologia Medica e Medicina Nucleare
Administrative Secretary, Prof. E. Conte, Ospedale Mauriziano, 10128 Torino, Italy. Meets annually.

Societas Radiologica Danica
Secretary, Dr. Bent Langenfeldt, Tretommervej 20a, DK. 8240 Risskov, Denmark.

Nederlandse Vereniging voor Radiologie
Secretary, Dr. J. D. Mulder, Dept. of Rad., Akademisch Ziekenhuis, Leiden, Netherlands.

Scandinavian Radiological Society
Secretary-General, Professor C. F. Unnérus, M.D., Hagalung-Tapiola, Havsvindsvägn 5 C., Finland. Annual Meeting.

Sociedad Española de Radiología y Electrología Médicas y de Medicina Nuclear
Secretary-General, Dr. Pilar Gallar Barberá, Villanueva, 11, Madrid 1, España. Meets every other Saturday evening of each month, Oct. to June, inclusive, in Madrid.

Sociedade Portuguesa de Radiologia e Medicina Nuclear
Secretary-General, Dr. Luís Aires de Sousa, Av. Elias Garcia, 123- 1, Esg.-Lisboa i-Portugal.

Schweizerische Vereinigung für Radiologie, Nuklearmedizin und Strahlenbiologie (Association Suisse de Radiologie, Médecine Nucléaire et de Radiobiologie)
Secretary, Dr. med. Gustav Schoch, Bethesdaspital, Gellerstrasse 144. 4000 Basel, Switzerland.

Asia

Indian Radiological Association
Honor. Gen. Secretary, Dr. S. P. Aggarwal, 10-B Kasturba Ghandi Marg. New Delhi 110001. 28th Indian Congress of Radiology will be held in Hyderabad in 1975.

Indonesian Radiological Society
Secretary, Dr. Gani Iljas Sasmitaatmadja, Radiology Dep., Faculty of Medicine, University of Indonesia, Salemba 6, Jakarta, Indonesia.

Iranian Radiological Society
Secretary, Dr. Majid Rooholamini, P.O. Box No. 14–1151, Teheran, Iran. The Society meets on the second Saturday of each month. 5th Iranian Congress of Radiology, Apr. 12–17, 1975.

Israel Radiological Society
Secretary, Dr. M. A. Lerner, Hesharon Hosp., Petah-Tigva, Israel.

Philippine College of Radiology
Secretary-Treasurer, Dr. Eduardo V. Nievera, Box 1284 Commercial Center, Makati, Rizal D-708, Philippines. Meets every second Thursday of the month.

Radiological Society of Thailand
Secretary, Prof. Rojana Suvansuthi, M.D., Ph.D., Depart. of Rad., Sirizaj Hospital, Faculty of Medicine, Mahidol University, Bangkok 7, Thailand.

Africa

Association of Radiologists of West Africa
Honorary Secretary, C. A. Beetlestone, M.B., B.S., D.M.R.D., Dept. Radiol., University College Hosp., Ibadan, Nigeria.

Radiological Society of South Africa
Secretary, Dr. B. Rosenberg, P.O. Box 3200, Johannesburg, South Africa.

South African International Radiological Congress
Director, Dr. Paul Sneider, P.O. Box 4878, Johannesburg, South Africa.

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ROENTGEN DIAGNOSIS

Head

Wolfstein, Ralph S., Tanasescu, Doina, Sakimura, Ivan T., Waxman, Alan D., and Siemsen, Jan K. Brain imaging with ^{99m}Tc-DTPA: a clinical comparison of early and delayed studies. *J. Nuclear Med.*, Dec., 1974, *15*, 1135–1137. (Address: Ralph S. Wolfstein, M.D., Division of Nuclear Medicine, Cedars-Sinai Medical Center, Cedars of Lebanon Hospital Division, 4833 Fountain Avenue, Los Angeles, Calif. 90029.)

Technetium 99m diethylenetriamine penta-acetic acid (DPTA) was used as the brain scanning agent in 126 patients. It was prepared from commercially available kits: 129 studies were done on 126 patients; 20 millicuries or smaller doses for children were given intravenously as a bolus injection following which perfusion studies were done, followed by static imaging at 30–60 minutes and repeated in 3–5 hours after the injection.

Seventy-eight of the studies were normal and 51 were abnormal, showing 55 lesions. Fifteen abnormalities could be seen only in delayed imaging. Nineteen abnormal areas were detected in at least 1 view of the early study which showed better in at least 2 views of the delayed study. Three arteriovenous malformations were best seen in the perfusion and early post-flow static imaging studies. They were only faintly seen in the delayed studies. Most of the lesions missed in the early imaging were infarcts. Other cases missed in the early imaging included encephalitis, a primary neoplasm, and a probable primary neoplasm.

The above studies demonstrated that no single time for scanning was optimum for all lesions, but that if early scanning was done, 27 per cent of the lesions would be missed and 62 per cent of the lesions were either more clearly seen or seen only with imaging at the 3–5 hour interval.—*Charles W. Cooley, M.D.*

Cheng, Vincent S. T., and Wang, C. C. Osteoradionecrosis of the mandible resulting from external megavoltage radiation therapy. *Radiology*, Sept., 1974, *112*, 685–689. (From: Department of Radiation Medicine, Massachusetts General Hospital, Boston, Mass.)

Records of 76 patients were reviewed for evidence of osteoradionecrosis of the mandible following curative megavoltage radiation therapy for tonsillar carcinoma. Sixty-three patients were free of local recurrence and were followed for 4 months to 12 years without the development of osteoradionecrosis of the mandible. Thirteen patients developed osteoradionecrosis without evidence of local recurrence.

The majority of patients were treated with a Co^{60} unit, 55 cm. source-to-axis distance. A midplane dose of 200–250 r, 5 days per week for 5–6½ weeks was given. Only 1 portal was irradiated on each treatment day when parallel opposing fields were used. Mandibular doses were calculated in rets. Eleven patients receiving a mandibular dose below 2,000 rets did not develop bone necrosis. Of the 13 patients with osteoradionecrosis, 12 received a mandibular dose over 2,100 rets. However, of the 63 patients without osteoradionecrosis, 41 also received over 2,100 rets mandibular dose.

Most of the patients with osteoradionecrosis were treated by single or 2:1 treatment portal loadings. Time of onset of symptoms ranged from 1 and 42 months. All eventually required hemimandibulectomy for control of symptoms.

Repeated infections dominate the clinical course of affected patients. Most are heavy smokers and drinkers with poor oral hygiene. Suggested contributing factors are carious teeth and teeth extraction, xerostomia, soft tissue ulceration, trauma, and incapacitating illnesses. Other radiation factors to be considered are dimensions of the jaw, size of treatment portals, and time-dose fractionation scheme.—*Odis D. Skinner, M.D.*

Newman, Harry, and Buschke, Franz J. Lethal midline granuloma: pathogenesis and radiation therapy. *Radiol. clin. et biol.*, 1974, *43*, 445–455. (Address: Harry Newman, M.D., Department of Radiology, Room 380-M, University of California, San Francisco, Calif. 94143.)

Lethal midline granuloma is a necrotic process affecting the nose and other portions of the upper respiratory system and eventually spreading to other organs. Since its first description in 1897 when it was described as "malignant granuloma of the nose," numerous other designations have been given; the authors supply a table of no fewer than 22 additional terms. Of far greater importance than nomenclature, is the confusion regarding the nature and significance of the process. An initial difficulty in any given patient is that an adequate amount of representative tissue is difficult to obtain by biopsy because of the massive tissue necrosis. Within the viable tissue, pathologists see granulomatous inflammation including lymphocytes, histiocytes, epithelioid cells and giant cells. Obliterating arteritis may also be present and is thought to be the basis for the intense necrosis. The ulcerative necrotic lesion may effectively mask a neoplastic process.

Six patients were seen and treated at this institution between 1955 and 1972. In all but 1 of these patients it was possible to establish a histologic diagnosis of lymphoma. Local response to irradiation was excellent, but 5 of the patients died of widespread disease. Other authors in the past have amassed a similar experience; *i.e.*, that a significant percentage

of patients with lethal midline granuloma have or shortly develop a malignant lymphoproliferative disorder. In addition these patients appear to lack normal resistance mechanisms and the lymphoma assumes a particularly violent, rapidly disseminated form.—*Rosalind H. Troupin, M.D.*

Neck and Chest

Schaposnik, Fidel, Varela, Omar W., and Barandica, Luis M. Neumoaxilografía. (Pneumoaxillography.) *Prensa méd. argent.*, April, 1974, *61*, 241–243. (From: Cátedra da Medicina Interna "D," Facultad de Medicina de la Plata, Argentina.)

The radiographic study of the axilla, after the injection of air, or CO_2, is an easy method to evaluate the axillary lymph nodes.

A scout (preliminary) roentgenogram is taken. After local intradermic anesthesia, the needle is inserted at the level of the fourth rib at its junction with the lateral margin of the pectoralis major. The needle is introduced within the axillary adipose tissue. A blood pressure cuff, whose upper margin is at the level of the inferior deltoid insertion, is then inflated to a pressure less than the systolic pressure (this will direct the air towards the axilla rather than allowing it to spread along the arm). Following this, 200 or 300 cc. of air are injected, and films (with the humerus abducted) are exposed; the plain study can be complemented by laminagraphic study. Both axillae should be studied for comparative purposes. The air is usually absorbed in 48 hours.

This examination is particularly useful in evaluating the axillary lymph nodes in obese patients in whom palpation is difficult.—*J. B. Alvarez, M.D.*

Gordonson, Jay, Birnbaum, William, Jacobson, George, and Sargent, E. Nicholas. Pulmonary cryptococcosis. *Radiology*, Sept., 1974, *112*, 557–561. (From: Department of Radiology, Los Angeles County-USC Medical Center, 1200 N. State Street, Los Angeles, Calif.)

Cryptococcus neoformans commonly occurs as a saprophyte on the skin and mucous membranes of man and other animals. The organism is found abundantly in pigeon as well as other avian excreta and in the soil. The respiratory tract is considered to be the common primary portal of entry. Following invasion of the lungs, the organism may remain localized or be disseminated hematogenously to any part of the body, particularly the brain, meninges, and spinal cord. Many patients suffering from cryptococcal meningitis present a history of antecedent pulmonary infection or show roentgenographic evidence of lesions in the lung. Factors that predispose to the pathogenicity of cryptococcosis include Hodgkin's disease, lymphosarcoma, leukemia, diabetes mellitus, and prolonged steroid therapy.

The typical lesion is composed of an aggregate of encapsulated fungus cells or colony of fungus cells held within a reticulum or lightly formed connective tissue which enlarges peripherally to compress adjacent tissues. An outstanding feature of the disease is the tendency to form masses composed almost entirely of organisms, which frequently show little or no inflammatory response. Such masses are usually discrete and frequently solitary, but may be multiple or even cavitate.

Twenty-six cases of pulmonary cryptococcosis are presented. The most common radiographic findings were single or multiple circumscribed masses or nodules in the upper lobes, which must be differentiated from neoplasms. Other less common radiographic manifestations include non-specific segmental pneumonias, cavitation, lymphadenopathy, pleural effusion, and generalized miliary disease.

Although pulmonary cryptococcosis is relatively uncommon, the diagnosis should be considered in any patient with meningitis and abnormal pulmonary roentgen findings.—*J. L. Montgomery, M.D.*

Govaerts, J. P., Engelholm, L., De Koster, J. P., Peeters, J. P., and Tombroff, M. Les pleurésies d'origine pancréatique. (Pleural effusions of pancreatic origin.) *Acta gastro-enterol. belg.*, June, 1974, *37*, 283–290. (Address: Dr. J. P. Govaerts, Avenue des Pagodes 292 B-1020 Bruxelles, Belgium.)

Direct demonstration of a fistula from the pancreas can explain certain large pleural effusions seen in association with pancreatitis. Most pleural effusions in pancreatitis are relatively small. Massive effusions with high amylase levels have generally been attributed to passage of pancreatic enzymes by a lymphatic route.

A 67 year old patient was found to have an infected fluid of pea soup consistency on an extensive left thoracentesis. Contrast wirsungography revealed a communication from the pancreas to the left pleural space. The empyema was secondary to a perforation of a pancreatic abscess into the pleura.

Two other patients, in their 30s, and alcoholics, had massive reaccumulating left pleural effusions containing a much higher level of amylase than their blood. Lipiodol injection into that pleural space showed communication to a subdiaphragmatic pseudocyst of the pancreas in each case. It was important to gradually stand these patients up during fluoroscopy to demonstrate the communication. In these 2 patients, chest tube drainage succeeded in the clearing of contents of both pleura and pseudocyst.

Thus, it is recommended that the lipiodol study of the pleural space be done early to recognize fistulas when a large pleural effusion with high

amylase level accompanies pancreatitis.—*Alan E. Oestreich, M.D.*

Liliequist, B., and Wiberg, A. Pedunculated tumours of the oesophagus: two cases of lipoma. *Acta radiol.*, July, 1974, *15*, 383–392. (From: The Departments of Neuroradiology, and Oto-Rhino-Laryngology, Umeå University, S-901 85 Umeå, Sweden.)

The roentgenologic changes in benign esophageal tumors differ from those caused by malignant lesions. Double contrast examinations and, recently, transverse tomography have been used to define the relationship between the tumor and the esophageal wall. The demonstration of a mass within the esophageal lumen is possible with the conventional technique with barium sulphate as the medium. The mucosa of the tumor as well as that of the esophageal wall are usually quite normal, although the folds are flattened or have disappeared due to dilatation of the esophagus harboring a large intraluminal mass. The surface of the mass may be grossly irregular due to its more or less lobulated shape, giving the impression that it is divided into 2 or more separate entities; the benign tumors are sometimes multiple, although a single lobulated growth is more common. No real obstruction to the contrast medium is usually encountered even when the tumor is of a huge size. This probably accounts for the relative lack of the symptoms in a significant number of patients. The growth is seen to be surrounded by a strip of contrast medium when examined in different positions and with rotation of the patient; the lower pole is usually well-demarcated.

The pedicle may be difficult or impossible to demonstrate even when the true nature of the lesion is known to the examiner beforehand. Misinterpretation of the condition as being due to cardiospasm may sometimes be avoided if the possibility of a large benign tumor is borne in mind. Negative endoscopy, even with a negative biopsy, may fail to eliminate a large benign intraesophageal tumor. It is possible to pass an esophagoscope down the esophagus in the presence of such a growth without detecting its presence. Furthermore, biopsy may prove negative as the mucous membrane covering the tumor is usually normal.—*David Morse, M.D.*

Boyd, Ronald M., Bogoch, Abraham, Greig, James H., and Trites, Edward W. Esophageal intramural pseudodiverticulosis. *Radiology*, Nov., 1974, *113*, 267–270. (Address: Ronald M. Boyd, M.D., 4095 Puget Drive, Vancouver, British Columbia, Canada.)

The authors report a single case of a 50 year old male patient with dysphagia followed for 9 years, who had radiographic findings of small barium projections from the esophagus. The literature on intramural diverticulosis and esophageal candidiasis is reviewed. The possible mechanisms and etiologies of the pouch-like projections are discussed.

In the initial description by Mendl of intramural diverticulosis, no biopsy material was available for confirmation of the radiologic findings. In this particular instance, the radiologic findings in the esophagus were compared with Rokitansky-Aschoff sinuses in the gallbladder. Hodes, in 1966, was the first to consider that the deep esophageal mucous glands were involved. At that time he postulated that a low-grade inflammatory process involved the esophageal glands, causing dilatation and hypertrophy of the esophageal mucous glands to cause the characteristic radiographic findings. Others have considered that the etiologic agent is *Candida albicans*. However, since *Candida* can be cultured from normal healthy individuals, it is the authors' opinion that it is an unlikely etiologic agent. Candidiasis is different radiologically from the intramural diverticulosis, as the outpouchings are somewhat larger, nonuniform and irregular.

Busch, in 1965, suggested that chronic inflammation with associated esophagitis could lead to obstruction of glandular ducts. The necks of the ducts become compressed by the edematous, inflamed mucosa and the duct ampullae are enlarged secondarily. The inflammatory process involving the ducts could also account for the motor abnormality according to the authors. However, the authors state "on the other hand, it is also possible that the localized inflammatory changes occur secondary to an abnormality of the mucous glands."

"Esophageal intramural diverticulosis" was the original terminology. The autopsy and pathology findings show that this term is inappropriate. The authors coin the phrase "esophageal intramural pseudodiverticulosis" as more descriptive.—*J. P. Eberts, M.D.*

Abdomen

Gonzalez, Giomar, and Kennedy, Timothy. Crohn's disease of the stomach. *Radiology*, Oct., 1974, *113*, 27–29. (From: Department of Diagnostic Radiology, University of Kansas Medical Center, Rainbow Boulevard at 39th Street, Kansas City, Kansas.)

Crohn's disease, a nonspecific granulomatous inflammatory disease affecting the ileum, jejunum and colon has been well known for many years. In 1949, Ross first documented involvement of the stomach by this disease. Since then only 34 cases of gastric Crohn's disease have been recorded in the English language literature and the authors in this article add 6 to this total number.

During the last 5 years 76 patients with a diagnosis of Crohn's disease of the gastrointestinal tract have been studied in the Department of Diagnostic Radiology at Kansas University Medical Center. Six of these patients were found to have involvement

of the stomach consistent with the presence of this disease and suggesting that Crohn's disease of the stomach is not as rare as previously indicated.

Two stages of the disease process can be identified roentgenographically. In the non-stenotic or inflammatory phase of the disease some hypertrophy of the mucosal folds and cobblestone appearance are frequently identified and there may be multiple small ulcerations. There is decreased peristalsis of the stomach, retained secretions and delayed emptying. The second stage, which is the stenotic or cicatricial phase, is characterized by a tubular, funnel shaped narrowing of the distal antrum often involving the pylorus and duodenal bulb. Complete obstruction of the gastric outlet may be associated with either of the phases.

The differential diagnosis of the gastric changes should include the more common possibilities of lymphoma, carcinoma, and diffuse eosinophilic gastroenteritis. Other less likely conditions that should be considered are: pancreatitis; tuberculosis; sarcoidosis; syphilis; and fungal disease such as histoplasmosis or actinomycosis. Other less common conditions are collagen diseases such as scleroderma, and amyloidosis, and reaction to foreign substances such as lye. The presence of Crohn's disease elsewhere in the gut does not necessarily mean that the findings in the stomach are also due to this disease, as it is well known that the incidence of peptic ulcer disease is increased in patients with Crohn's disease.

Endoscopic examination of the stomach and duodenum is a helpful adjunct in the diagnosis of this condition. The value and safety of biopsy, however, is controversial, since the disease is intramural and a deep biopsy would be required to obtain a satisfactory specimen.

It is the opinion of the authors that involvement of the stomach with Crohn's disease is not rare. It is evident from this study that, while there is no single characteristic roentgenographic pattern of gastric Crohn's disease, any change in the normal anatomy of the stomach should suggest involvement, especially in patients in whom this disease has been found in the small bowel and/or colon.—*Donald N. Dysart, M.D.*

Williams, Christopher B., Hunt, R. H., Loose, H., Riddell, R. H., Sakai, Y., and Swarbrick, E. T. Colonoscopy in the management of colon polyps. *Brit. J. Surg.*, Sept., 1974, *61*, 673–682. (From: Saint Mark's Hospital, London, England.)

Colon polyps are important because they may be a source of frank blood loss, may be associated with abdominal symptoms, and there is evidence that polyp to cancer sequence is not uncommon.

The use of colonoscopy in the management of colon polyps at St. Mark's Hospital in London is the subject of this report. Patients there were examined with the colonoscope only after a Malamö air contrast barium enema. However, the authors note that more than half of their patients were referred from other hospitals and these patients almost always had had only a conventional barium enema without air contrast studies prior to their admission.

Bowel preparation is extremely important and is probably as important in preparation for colonoscopy as is good preparation for a barium air contrast enema study. Both Olympus and ACMI colonoscopes were used. The use of the new American Cystoscope Makers' Instrument #F9-A was found particularly helpful, because it made possible both retrieval and removal of the polyps easier.

The policy of diagnostic or therapeutic use of colonoscopy should not be made quickly. It is a long procedure frequently requiring more than 1 hour of time, and the removal of polyps, subsequently shown to be malignant, makes it somewhat questionable as to the necessity of segmental resection or merely subsequent follow-up studies. The costs are great and in experienced hands the hazards are acceptable. High quality roentgenographic studies justify radiologic rather than colonoscopic follow-up studies.

The experience at St. Mark's Hospital in London seems to represent a major advance in the management of colon polyps.—*Richard E. Kinzer, M.D.*

Suzuki, Takashi, Kitagawa, Susumu, and Honjo, Ichio. Role of splenic arteriography in evaluation of malignant tumors in the body of the pancreas. *Surg., Gynec. & Obst.*, Oct., 1974, *139*, 509–513. (From: The First Department of Surgery, Kyoto University Medical School, Kyoto, Japan.)

This group of investigators has recently begun to use splenic arteriography in evaluation of carcinoma of the pancreas. While recognizing that tumors confined to the capsule of this organ are difficult to diagnose, it was felt that splenic arteriography would be helpful depending on the degree of invasion by the tumor.

Four roentgenographic patterns were recognized: the normal appearing splenic artery; the smooth tapering type; the rough tapering type; and the obstructed type.

Ten patients were found to have tumors that were considered to be expansile in type, 3 of which had normal appearing splenic arteries and 7 of which exhibited smooth tapering. Nineteen patients had infiltrative tumors, 13 of whom exhibited the rough tapering appearance and 6 of whom exhibited arterial obstruction. All of the patients who were evaluated had proven tumor. Presenting clinical symptoms, laboratory findings and laparotomy findings were discussed.

The authors point out that most studies published to date provided little information as to clinical cor-

relation of splenic arteriography with symptoms and signs, operative findings, and resectability of the lesion. It was suggested that the ductal cell carcinoma types correlated best with tumors that tended to invade the surrounding tissues. Tumor vaculature was closely related to the angiographic pattern with cystadenocarcinoma, islet cell carcinoma and sarcoma showing increased vascularity. Infiltrative tumors appeared to be quite hypovascular. Most of the expansile tumors were associated with liver metastases, while the infiltrative types often showed peritoneal dissemination. Survival correlation revealed that the prognosis was unfavorable in the rough tapering type, but the smooth tapering type tended to do better with resection of the main tumor. Correlation with the incidence of diabetes mellitus suggested that those in whom the splenic artery showed obstruction were more likely to have elevation of the fasting blood sugar. Diabetes as an early manifestation of cancer of the pancreas is, therefore, considered to have little meaning.

In the summary the authors point out that normal and smooth tapered splenic arteries are most likely associated with nonductal cell carcinoma and that rough tapering and obstructed lesions found in the splenic artery were most likely in the ductal cell group. The longest survival period and highest percentage of resectability were in patients with normal appearing splenic arteries and the poorest prognosis in those with obstruction. Hyperglycemia and severe lumbar pain were frequent in those with the obstructed pattern, but no significant difference in serum amylase, abdominal pain and weight loss could be found.

Splenic arteriography is considered to be a useful method in the evaluation of patients with cancer of the pancreas.—*R. P. Andrews, M.D.*

Bean, William J., Smith, Stover L., and Calonje, Mario A. Percutaneous removal of residual biliary tract stones: problems encountered in a series of 44 cases. *Radiology*, Oct., 1974, *113*, 1–9. (From: Department of Radiology, East Jefferson General Hospital, 4200 Houma Boulevard, Metairie, La.)

Residual biliary calculi are frequently discovered following cholecystectomy, and thus pose a significant medical problem. A safe method of non-operative stone removal would be more desirable than further surgery. The successful methods previously used include irrigation of the duct system with various solutions, use of extraction forceps, and push-through catheters. The Dormia basket was first used successfully in 1969 for a percutaneous extraction procedure and, since that time, has become an accepted and useful procedure.

The authors present a timely report of their experience with basket retrieval of biliary calculi in 44 patients with a brief description of their technique and a discussion of the various problems encountered along with suggestions for overcoming these problems.

The technique is based on the presence of an indwelling drainage catheter, usually a T-tube, which should have been in place for 4 to 6 weeks. This time period is required for the development of a well formed fibrous tract around the tube. Initially, the authors introduce a No. 6 French Teflon catheter, with a protruding J guidewire, through the T-tube and into the common duct or common hepatic duct, traversing either a limb of the T-tube or the central notch in the tube. Usually, slight traction on the T-tube will change the limbs from a T to a Y configuration, assisting the introduction. If traversing the tube proves difficult, or the tube is too small, the T-tube can be removed and the residual fibrous tract negotiated with a soft rubber catheter, a J guidewire and a catheter, or a controllable tip catheter. Once the catheter is in place, the wire basket can be inserted, advanced to an open position at the level of the stone, and the stone snared, and subsequently retrieved.

The usually surmountable problems encountered in this group of patients were related to the size, position and configuration of the T-tube, the anatomic features of the patient's biliary duct system, and the size, number and location of residual calculi.

The extremely tortuous T-tube tract complicates retrieval, since the tortuosity produces lack of control of the basket or J wire, allowing a success rate of only 25 per cent in such patients. One solution offered is progressive dilatation of the tract, to accommodate a No. 14 French straight catheter which tends to straighten the T-tube tract. Occasionally, a limb of the T-tube is found to be in the cystic duct remnant, which is no problem if the residual stone is in the distal common duct. However, retrieval is nearly impossible if the stone is in the hepatic duct. Loss of the T-tube or catheter is usually no problem if retrieval is attempted within 24 hours, but at 48 hours, the authors have been unable to negotiate the nearly closed fibrous tract.

The anatomic features of an angulated common duct presents a special problem, as a straight catheter and basket tend to press against the medial wall of the distal common duct, thereby courting perforation. This problem is easily solved by the use of a 180 degree pre-curved Teflon catheter. However, the presence of operative strictures in the common duct is a more difficult problem but, usually, the narrowed area can be negotiated with pre-curved catheters, or the use of a controllable tip guidewire.

The presence of multiple stones does not create a problem if infection is not present and the fibrous T-tube tract is firm, even though the biliary tree must be catheterized for each stone. If stones are lodged in opposite portions of the duct system, the T-tube usually must be removed first. Large stones, larger than the T-tube tract, can be extracted by

either fragmenting the stone into smaller particles, permitting particle removal, or successively dilating the T-tube tract, permitting the removal of the intact stone. The standard basket measures 38×16 mm. and will readily retrieve a stone 10 mm. in diameter. A larger basket is available. Stones lodged in the biliary radicles can usually be retrieved by a standard basket if the ducts are large and straight. If not, they can be retrieved with a small half-sized (20×8 mm.) basket.

The complications in this group of 44 patients were noted to be minor, and consisted of 2 instances of common duct perforation near the ampulla, 2 instances of transient hypotension, and a perforation of the peritoneal cavity in 2 patients. All patients tolerated these complications.

A serial tabular record of these patients indicates a success rate in 33 of the 44 patients, but even this laudable success is misleading since a majority of their failures occurred in the first 14 patients. The reviewer notes only 5 failures in the last 30 patients in this series! Radiologists skilled in vascular catheterization will find it quite easy to perform stone removal through the T-tube tract. The insertion of a larger T-tube by the surgeon is recommended, especially if there is any suspicion that residual biliary stones are present.

The authors reasonably conclude that basket retrieval or fragmentation is a safe, useful, and considerate method of clearing the biliary tree of residual stones found after gallbladder or biliary tract surgery.—*Edward B. Best, M.D.*

Schraibman, I. G. Non-parasitic liver abscess. *Brit. J. Surg.*, Sept., 1974, *61*, 709–712. (From: The Infirmary, Rochdale, Lancs, England.)

Liver abscess is not uncommon in tropical areas and is associated with parasitic infection. However, in Britain, the condition is infrequent and is usually pyogenic in nature.

The author observed 3 pyogenic liver abscesses within a 6 month period and this moved him to study the condition. Fifteen proven cases of non-parasitic liver abscess from the Manchester region were discovered in a survey of 848,861 patients' records. The presenting clinical signs in all of these patients included abdominal pain with fever, chills, weight loss, diarrhea, nausea and vomiting, clinical jaundice, and a palpable liver. Bile chemical investigations were rather limited and the author points out that liver scans were done in only 4 of the 15 patients, but all of these showed a filling defect in the liver. Seven of the 15 patients died and in none of these was the diagnosis suspected before death. Biliary tract infection seemed to be the source of the abscess in many of the cases recorded. In Ochsner's review in 1938, appendicitis caused 34 per cent of the liver abscesses with the infection spreading *via* the portal vein.

Classification of the liver abscesses is attempted and the author divides them into 3 major groups: (1) a single large abscess without an apparent preliminary abdominal cause; (2) large abscess which is usually single but follows or is associated with intra-abdominal disease; and (3) multiple small abscesses which occur in patients who are severely ill from other diseases.

The conclusion is drawn that in the Type 1, single large abscess, recovery is common, if diagnosis is made and the abscess is drained. In the Type 2, usually single large abscess, recovery should be expected, if the abscess is drained; in the Type 3, multiple small abscess cases, one should expect a fatality, since the diagnosis cannot usually be made.—*R. E. Kinzer, M.D.*

Cline, Ross L. Matallana, Raul H. and Crummy, Andrew B. Percutaneous transhepatic cholangiography. *Australasian Radiol.*, June, 1974, *18*, 191–197. (Address: Andrew B. Crummy, M.D., The Department of Radiology, University of Wisconsin Center for Health Sciences, 1300 University Avenue, Madison, Wis. 53706.)

The difficulty in distinguishing between obstructive and hepatocellular jaundice is a great clinical problem. Most roentgen studies, including intravenous cholangiography, are useless in the patient who has nonhemolytic jaundice. However, percutaneous transhepatic cholangiography can be very useful.

This procedure was first reported in 1937 and is still underutilized. The development of less toxic contrast agents, better instruments, and more experience has made this examination quite acceptable.

The authors prefer the lateral approach because of the greater precision obtained with the horizontal direction of puncture and in order to minimize the possible complications of bile peritonitis. The site of the puncture is at the mid axillary line in the 8th or 9th intercostal space. One per cent Xylocaine is used for local anesthesia including the liver capsule. An 8 inch 18 gauge teflon catheter needle is used. This needle is flexible and once the inner metal stylet is removed it provides a distinct advantage in that respiration does not tear the liver capsule or parenchyma. When bile has been obtained, it is aspirated and Renografin 60 is injected under fluoroscopic observation.

The authors' report discusses 60 patients with 63 cholangiographies attempted and 39 satisfactory studies obtained. The causes of obstructive jaundice in 35 patients is listed in Table II and shows 11 with pancreatic carcinoma and 10 with bile duct carcinoma.

The article is accompanied by numerous very nice illustrations.

The conclusion is drawn that this is a safe and

useful radiologic procedure for evaluation of the jaundiced patient. The authors state that an unsuccessful percutaneous cholangiogram is suggestive evidence that obstruction is not present.—*Richard E. Kinzer, M.D.*

Nervous System

Hilal, Sadek K., Marton, Dominique, and Pollack, Edward. Diastematomyelia in children: radiographic study of 34 cases. *Radiology*, Sept., 1974, *112*, 609–622. (From: The Departments of Radiology, College of Physicians and Surgeons, Columbia University, The Neurological Institute, New York, N. Y.)

In 1837 Ollivier coined the word diastematomyelia (Greek diastema: cleft; and myelos: medulla or spinal cord). The authors have adopted the following broad definition: diastematomyelia is a congenital anomaly in which the spinal cord or the filum terminale or both are split, dorsoventrally, into 2 parts usually separated by a septum.

In 1940 Lichtenstein introduced the term "dysraphyism" to cover the conditions with incomplete fusion of the midline embryonic structures. Occult dysraphyism includes: (a) diastematomyelia; (b) congenital intraspinal mass lesions such as neurenteric cysts, dermoid cysts and teratomas; and (c) abnormalities of the spinal cord and the medullary conus associated with occult spina bifida such as a low conus and intraspinal lipomas.

The 2 parts of the spinal cord which are divided by the septum are unequal in their cellular and neuronal content, so that they represent neither 2 half spinal cords nor 2 spinal cords in parallel. The duplicated cords are somewhat similar to definitive cords with 4 gray columns, 2 ventral and 2 dorsal, with 1 pair lateral and 1 pair medial. Usually a significant asymmetry is observed between the 2 sides of the split cords. The medial roots are usually absent or poorly developed while the lateral roots are well formed.

The pathoanatomic features of diastematomyelia may be summarized as follows:

1. Spina bifida, usually of the occult type.

2. Anomalous spinal canal showing dilatation at the level of the cord duplication and a variable degree of partial doubling of the canal as manifested by an osseous or osseocartilaginous process projecting into the spinal cord canal or by a band of fibrous tissue between the two cords.

3. Vertebral anomalies consisting of underdevelopment or absence of derivatives of ossification centers.

4. Duplication of the meninges, usually the pia mater. The dura is duplicated in approximately 50 per cent of cases.

5. The level of the spur and the cord doubling is usually lower than the mid-dorsal level.

6. Congenital midline tumors such as dermoid cysts and neurenteric cysts are sometimes found at the level of the spur.

7. The embryologic basis of diastematomyelia is believed to be a defect affecting all 3 germ layers. There is continued infolding of the neural tube yielding 2 neural tubes with subsequent condensation of mesodermal tissue between the 2 tubes.

Radiographic evaluation should include plain radiography of the spine in multiple views as well as myelography. Tomograms are most useful in establishing the diagnosis in patients in whom the bony spur is difficult to appreciate because of its minimal calcification or because of severe deformity of the spine. In the absence of the bony spur the definitive diagnosis of diastematomyelia can only be made by myelography. Cisternal puncture for instillation of contrast material in the myelogram is preferred to the lumbar puncture in all patients with congenital anomalies of the lumbosacral spine. Patients should be examined in both prone and supine positions and enough opaque medium used to cover 5 to 6 vertebral bodies.

This study evaluates the radioanatomic and clinical features of 34 children below the age of 18. Abnormal gait was the most common presenting feature in this series. Others presented with unilateral or bilateral leg weakness or muscle atrophy; leg length discrepancy; abnormal lower extremity reflexes; abnormal foot length or foot deformities. Frequently there was a cutaneous abnormality on the back such as a patch of hair, a nevus, or a skin dimple. Some children had urinary or fecal incontinence. The combination of a limb deformity and incontinence is most suggestive of an anomaly of the caudal end of the spinal cord. Thirty-two of the 34 patients were girls.

Myelographically, the septum appears as an area devoid of contrast material at or near the center of the subarachnoid sac. The bony spur, if present, can usually be seen within this area. The two "halves" of the spinal cord and the conus medullaris can be readily identified on myelography as an area of reduced density within the opaque column on either side of the septum.

Of the 34 cases, 15 had no scoliosis. Seven had moderate scoliosis and 12 had severe scoliosis. The data indicate that the chance of scoliosis developing increases significantly the longer the patients are left without treatment.

Anomalies of posterior vertebral elements are very common in diastematomyelia. Only 3 of the 34 cases had no anomalies of the posterior elements. The most common finding was anomalous laminae. In most cases there is a fusion in the vertical direction involving the laminae of 2 or more segments which is frequently associated with a variable degree of spina bifida. The combination of vertical fusion of laminae with spina bifida at the same level or at an adjacent level should raise a strong suspicion for diastemato-

myelia. Prominent spinous processes and anomalies of the pedicles were also seen.

Twenty-nine of the 34 patients had anomalous vertebral bodies. The deformities varied from simple narrowing of the intervertebral space to the complete fusion of multiple segments. One of the most common anomalies was the narrowing of the vertebral bodies in the anteroposterior direction which was encountered only at the level of the spur. Partial or complete splitting of the vertebral bodies in the sagittal plane and hemivertebral hypoplasia or agenesis were also common findings in this group of patients.

The recognition of diastematomyelia in patients with and without scoliosis is important because of the necessity to institute proper management. This study suggests that in undiagnosed children with diastematomyelia, scoliosis tends to develop later in life.—*J. F. Bergstrom, M.D.*

Irstam, L., Sundström, R., and Sigstedt, B. Lumbar myelography and adhesive arachnoiditis. *Acta radiol.*, July, 1974, *15*, 1356–368. (From: The Departments of Diagnostic Radiology II, Sahlgrenska Sjukhuset, S-413 45 Gothenburg, and Diagnostic Radiology, Centrallasarettet, S-551 85 Jönköping, Sweden.)

Several reports of adhesive arachnoiditis as late sequelae after lumbar myelography with water-soluble contrast media have appeared in recent years. Six hundred and ninety-four patients were primarily examined with methylglucamine iothalamate (Conray 60) and 800 patients were examined with methiodal (Kontrast U).

Adhesive arachnoiditis was much more common after myelography with Kontrast U than after myelography with Conray 60. Surgery following Kontrast U myelography raised the incidence of a later adhesive arachnoiditis; this is not observed following Conray 60. The results indicate that patients already having adhesive arachnoiditis should not be further examined with lumbar myelography, except for exclusive indications and then never with Kontrast U.—*David Morse, M.D.*

Skeletal System

Teplick, J. George, Eftekhari, Farzin, and Haskin, Marvin E. Erosion of the sternal ends of the clavicles: a new sign of primary and secondary hyperparathyroidism. *Radiology*, Nov., 1974, *113*, 323–326. (From: The Department of Diagnostic Radiology, Hahnemann Medical College and Hospital, Philadelphia, Pa.)

The authors present 12 cases of hyperparathyroidism with erosion of the sternal ends of the clavicles. Ten of these patients had secondary hyperparathyroidism from renal osteodystrophy. Two patients had primary hyperparathyroidism. The finding is presented as a new sign; it can be defined on properly positioned and properly exposed routine posteroanterior chest roentgenograms. The addition of lordotic roentgenography and tomography will permit better detailing of the sternal ends of the clavicles.

The erosive change is noted by the loss of the sharply defined thin, dense white subchondral line of the medial ends of the clavicles. The resorption of the bone occurs in the subchondral portion of the clavicles. If the erosion occurs prior to the closure of the epiphyseal growth plate, findings of renal rickets in the metaphyseal portion of the clavicle can occur.

Erosive changes in the sternal ends of the clavicles have been reported in rheumatoid arthritis, scleroderma, and rarely in cases of gout, Reiter's syndrome and ankylosing spondylitis.

The authors give credit, in the footnote of the paper, to Griffiths, H. J., and Ozer, H., who published a paper discussing the same findings in the *Journal of the Canadian Association of Radiologists*, December, 1973, *24*, 334–336.—*J. P. Eberts, M.D.*

Weber, David A., Keyes, John W., Jr., Benedetto, William J., and Wilson, George A. ^{99m}Tc pyrophosphate for diagnostic bone imaging. *Radiology*, Oct., 1974, *113*, 131–137. (From: Department of Radiology, Division of Nuclear Medicine, University of Rochester, School of Medicine and Dentistry, Rochester, N. Y.)

Various phosphorus containing compounds, labelled with Tc^{99m}, have increased the scope and number of bone imaging procedures because of their apparent advantages over radioactive strontium and fluorine. The most obvious advantages are directly related to the technical and economic aspects of the label, Tc^{99m}. This paper concerns itself with the more scientifically erudite aspects of the use of one such compound, Tc^{99m} pyrophosphate. *In vivo* distribution and kinetics were derived from conventional image displays and quantitative computer analyzed image data. *In vitro* kinetics were derived from blood and urine radio-assays. The information was gathered from studies performed on 30 adult patients and 8 New Zealand White Rabbits.

The radiopharmaceutical was prepared by adding 1–10 ml. of Tc^{99m} pertechnetate eluate to a multidose vial containing 15.4 mg. of stannous pyrophosphate, and in the course of the study 3 different lots of lypholized stannous pyrophosphate were used. Thin layer chromatography on each batch prepared exhibited binding efficiencies greater than 90 per cent, and pH values were consistently in the 7.0–7.1 range. Intravenous injections of 10 millicuries to adult patients, and 0.5–1.0 millicuries to rabbits, were made within 2.5 hours of preparation. There was less than 0.7 mg./mc of stannous pyrophosphate in every injection.

The rabbits were studied on the gamma camera only. Four rabbits were imaged hourly for the first 5 hours postinjection, and the other 4 were imaged at 1, 3, and 5 hours only. No anesthesia was used. Good resolution and detail of the entire rabbit skeleton were always obtained.

The patients received more intensive studies. Pre- and postinjection blood pressure, pulse, and respiratory recordings were made on all. Fifteen had a battery of hematologic studies and blood and urine chemistries run at 24 and 48 hours postinjection. Five patients had 24 hour urine samples collected from which radioactivity assays were made for dosimetric considerations, and submitted blood samples at $\frac{1}{4}$, $\frac{1}{2}$, 1, 2, 3, 4, 5, and 24 hours from which base line curves of clearance of radioactivity were generated. There were no significant changes in vital signs from pre- to postinjection. The hematologic and chemical studies revealed no alterations. The average 24 hour urine assay showed that 38.2 per cent of the administered dose was excreted, and that the plasma levels of radioactivity fell from 4 to 1.3 per cent of the administered dose per liter in the first 5 hours, and down to 0.9 per cent at 24 hours.

All patients received anterior and posterior 5:1 minification scanning beginning 3 to 4 hours postinjection. A 20 KeV window was centered over the 140 KeV photopeak; a 163 hole, 5 inch focal, low-energy collimator was used; $\frac{1}{4}$ to $\frac{1}{8}$ inch rasters were run; and a maximum of 85 counts/min./cm. were obtained at a speed of 525 cm./min. Good quality scans were consistently obtained.

Twenty-five patients had one set of gamma camera images recorded between 3 to 4 hours postinjection, and the other 5 had gamma camera images 1 to 2, 3 to 4, and 5 to 6 hours postinjection over symptomatic or other selected sites. A 25 per cent window over the 140 KeV photopeak was set, a 15,000 hole high resolution collimator was used, and all gamma camera images were digitized in a 64×64 computer matrix and stored on magnetic discs for later retrieval and quantitative analysis. Good quality gamma camera images were consistently obtained also.

Seventeen of the patients showed abnormal areas of concentration of radioactivity, and comparison of rectilinear scans and gamma camera images revealed no disparity in detection between the two methods. The rectilinear scans provided better anatomic continuity, and gamma camera images provided better skeletal detail.

The serial gamma camera images obtained from 5 patients were further analyzed to evaluate relative biological clearance rates between bone and soft tissue to assist in determination of optimum imaging times. These determinations, plus the demonstration of relatively long biologic turnover times for proven metastatic bone lesions, suggest that image improvement could be obtained by delaying imaging for 5 to 6 hours postinjection. However, a fairly severe decrement in count rate occurs.

Utilizing data obtained from urine, blood, and *in vivo* analyses, absorbed radiation dose to certain organs was calculated by the absorbed fraction method. This varied from a low of 50 millirads/10 millicuries in the liver to a high of 910 millirads/10 millicuries in the urinary bladder.—*F. C. Petty, M.D.*

Merchant, Alan C., Mercer, Richard L., Jacobsen, Richard H., and Cool, Charles R. Roentgenographic analysis of patellofemoral congruence. *J. Bone & Joint Surg.*, Oct., 1974, *56-A*, 1391–1396. (Address: Alan C. Merchant, M.D., 2500 Hospital Drive, Mountain View, Calif. 94040.)

There is a confusing variety of methods for making roentgenograms of the patellofemoral joint in axial projection—the "sunset" or "sky-line" view. Because of the various disadvantages of other techniques a simple, accurate and reproducible method for clinical use was devised.

The patient is placed supine on the roentgenographic table with the knees flexed 45° over the end. The knees are slightly elevated to keep the femora horizontal and parallel with the table surface. This allows the roentgen tube and collimator to be raised over the patient and angled down 30° from the horizontal, providing a beam-to-femur angle of 30°. The film cassette is placed about 12 inches below the knees resting on the shins and perpendicular to the roentgen ray beam. The legs are strapped together at about calf level to control rotation and both knees are exposed simultaneously.

The sulcus angle is the angle formed by the highest points on the medial and lateral femoral condyles and the lowest point of the intercondylar sulcus. The depth of the intercondylar sulcus, measured by the sulcus angle, is the most important factor in distal femoral dysplasia in patients with recurrent dislocation of the patella. The actual height of the lateral femoral condyle is only significant as it relates to the depth of the sulcus. The average sulcus angle is 138° (range 126–150°; standard deviation, 6°) as determined using the authors' technique. The congruence angle was developed in order to devise an objective method of measuring the relationship of the patella to its intercondylar sulcus. To make this measurement the sulcus angle is bisected to establish a zero reference line. A second line is then projected from the apex of the sulcus angle through the lowest point on the articular ridge of the patella. The angle measured between these 2 lines is the congruence angle. If the apex of the patellar articular ridge is lateral to the zero line, the congruence angle is designated positive; if it is medial, the congruence angle is negative. The average congruence angle in 100 normal subjects was −6°, with a standard deviation of 11°. Therefore, it was determined that any congruence angle greater than +16° is abnormal at the 95th percentile.

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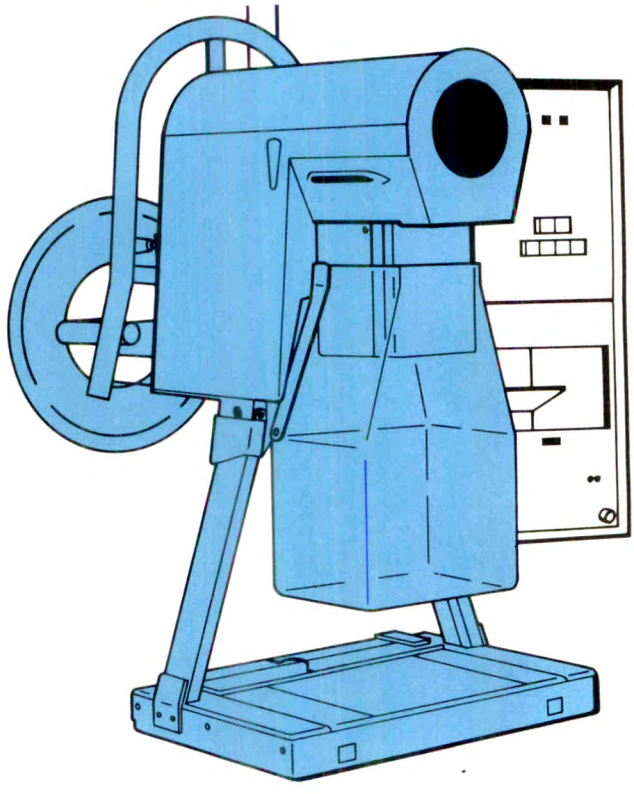

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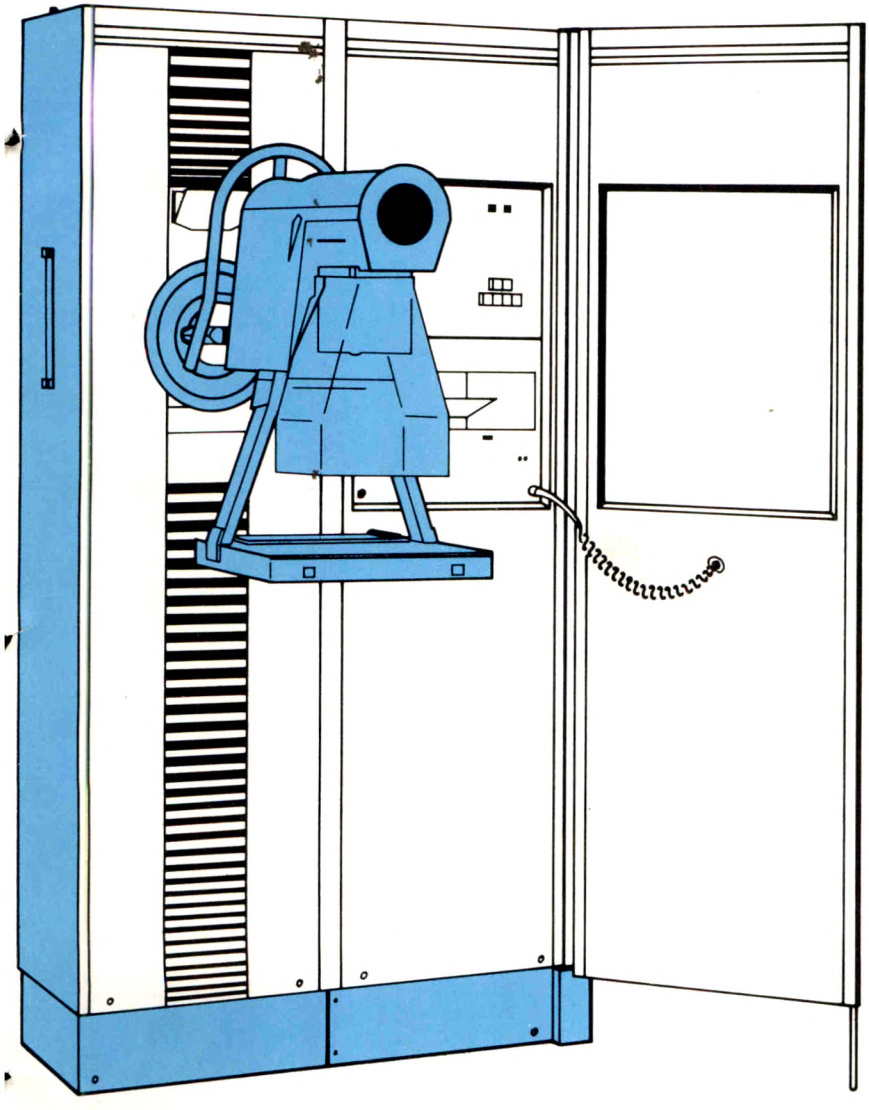

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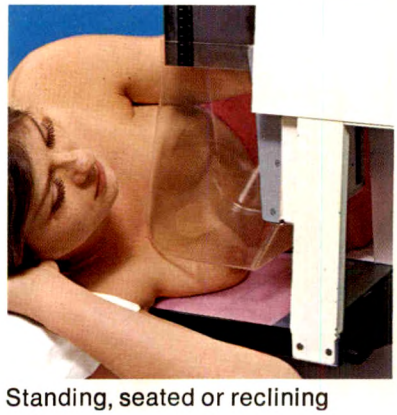

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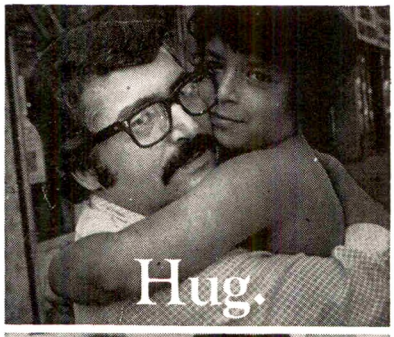

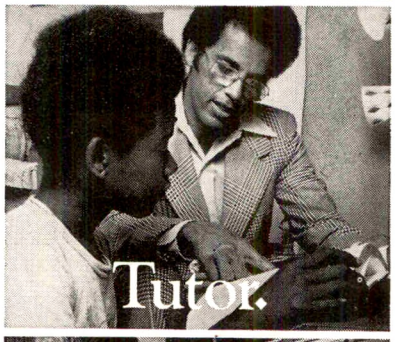

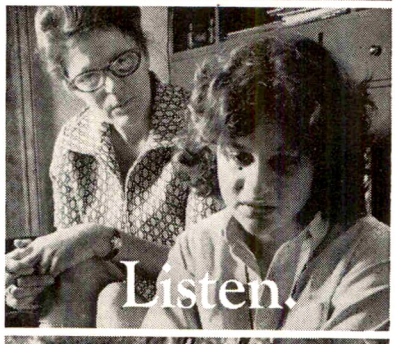

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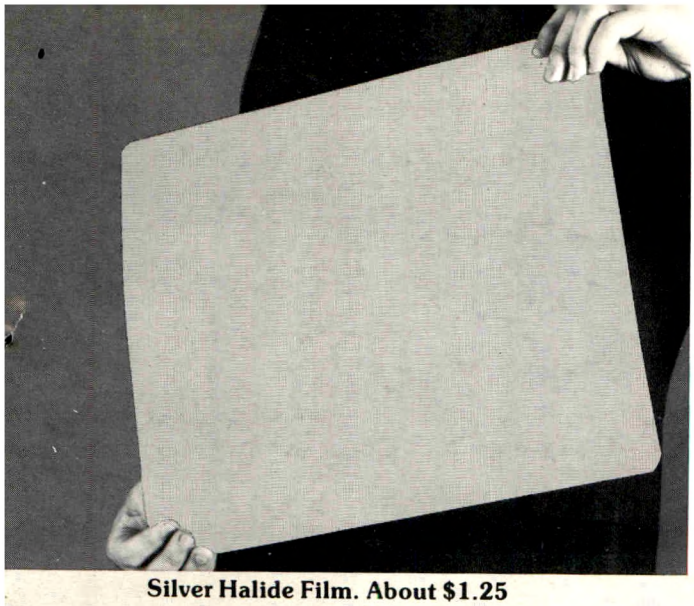

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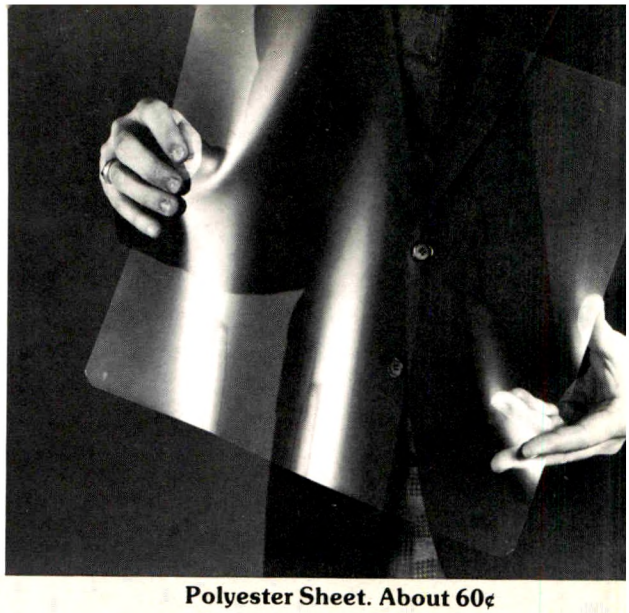

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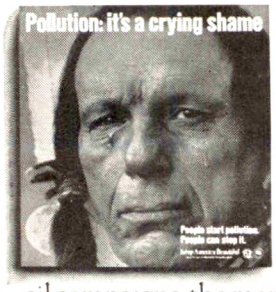

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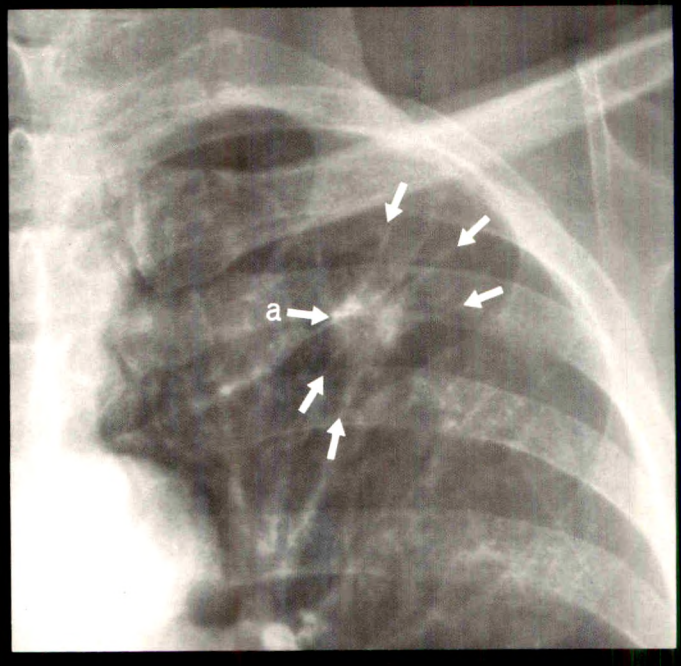
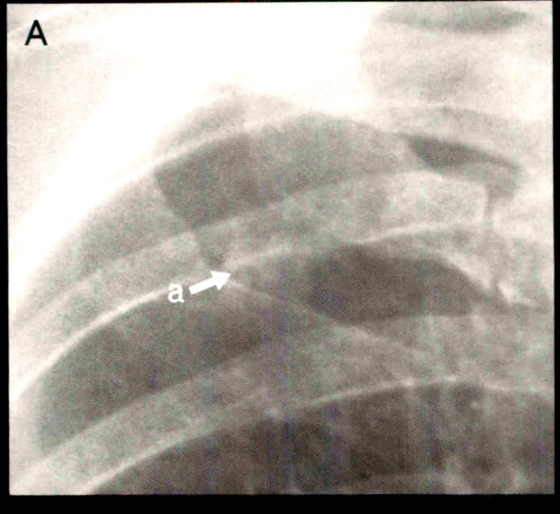
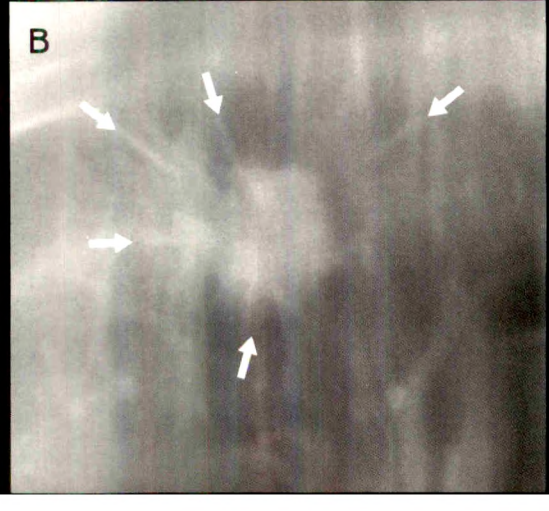


CASE I—This 50-year-old woman was a heavy smoker who had no complaints.

The solitary pulmonary nodule in the left upper lobe reveals a peripherally placed calcific deposit (a) (proven healed tuberculosis), plus numerous pseudopoda (arrows) streaming perifocally.



CASE II—This 53-year-old heavy smoker had a chronic nonproductive cough. His routine roentgenogram, Fig. A, reveals an indistinct solitary pulmonary nodule in the right upper lobe (a) with pseudopoda demonstrated by tomography, Fig. B (arrows).



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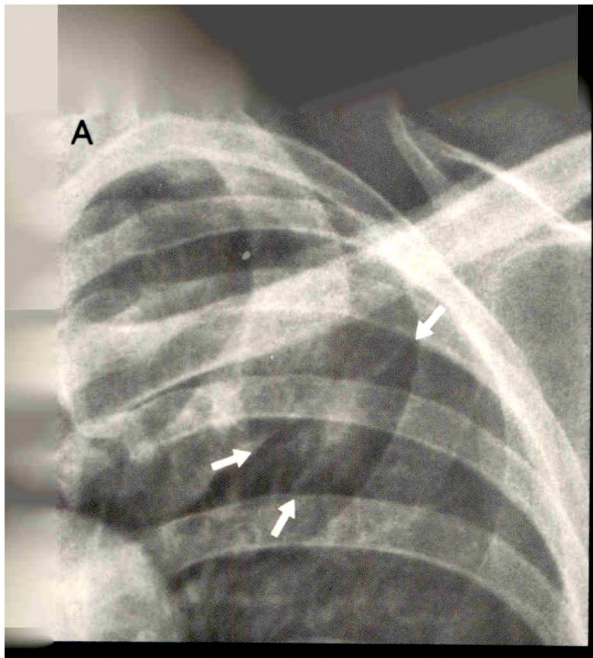
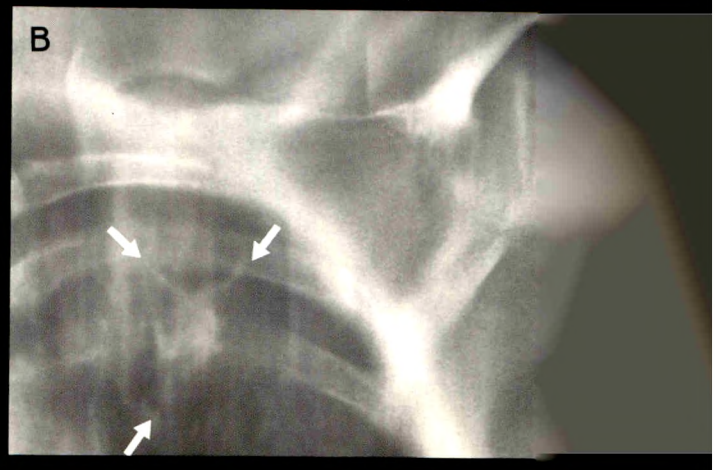
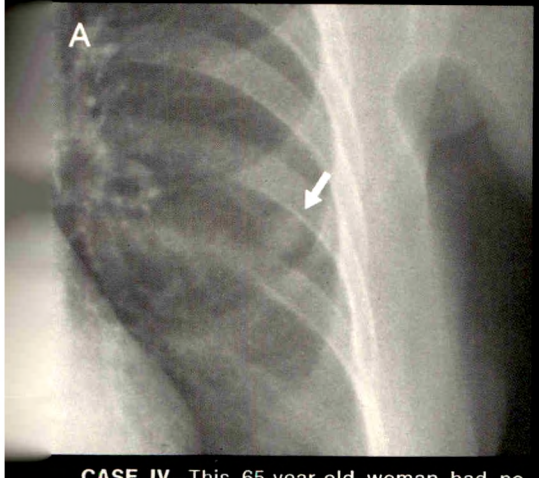


CASE III—This 71 year old man had no symptoms referable to the chest.

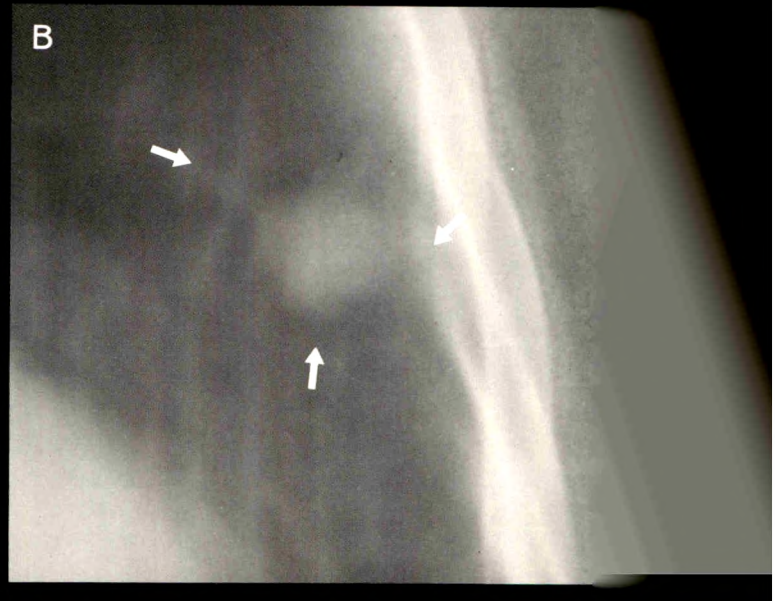
For 16 months the radiologist repeatedly reported "probable carcinoma of the lung;" finally the lesion was removed.

Pseudopoda (arrows) visible in the left upper lobe in the routine exposure, Fig. A, are more clearly depicted by tomography, Fig. B (arrows).





CASE IV—This 65-year-old woman had no complaints. In her routine exposure, Fig. A, a small pulmonary nodule (arrow) was seen, which revealed barely perceptible pseudopoda (arrows) in the tomographic study, Fig B



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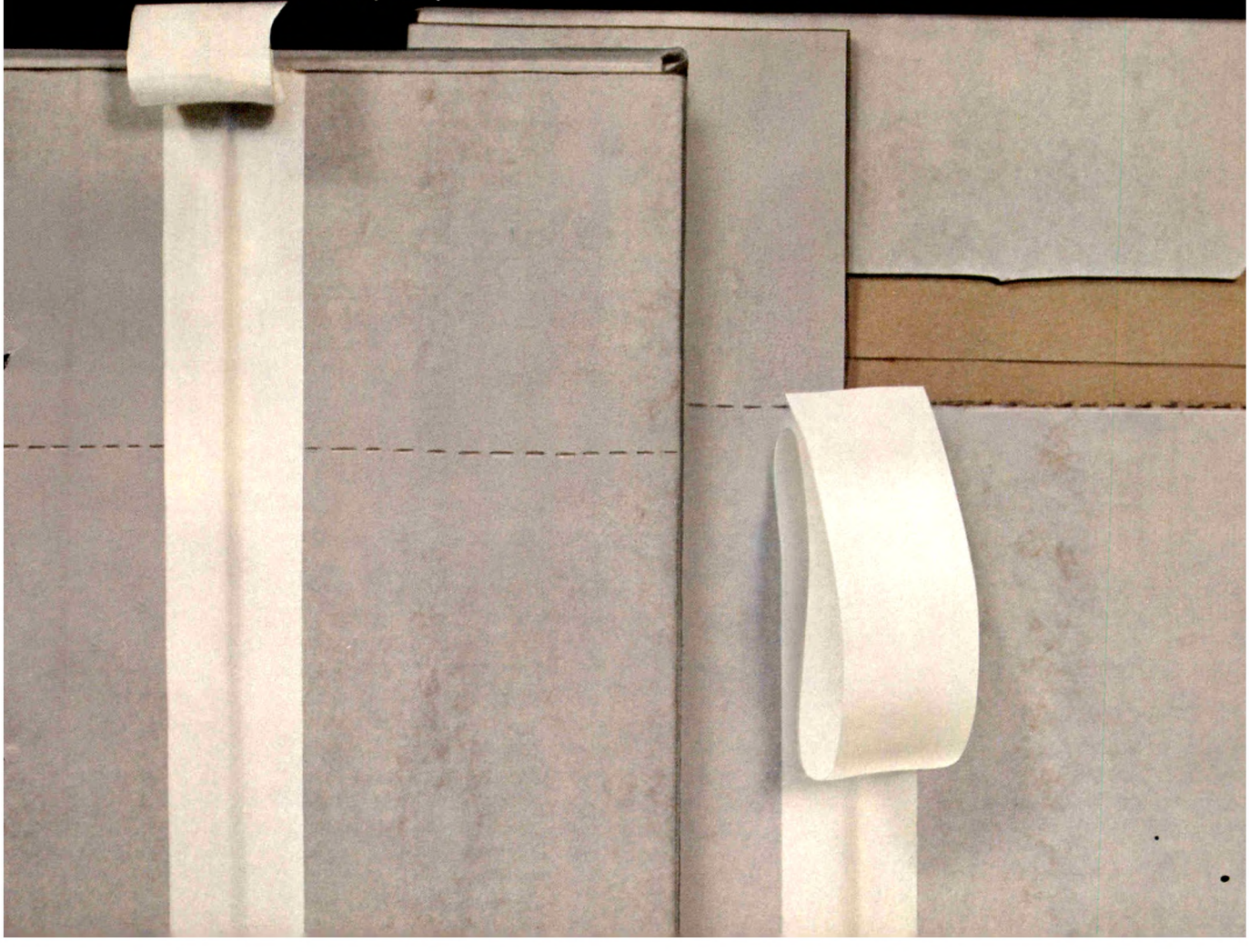

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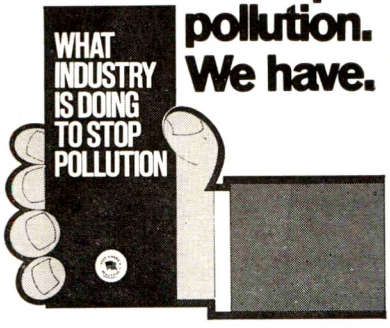

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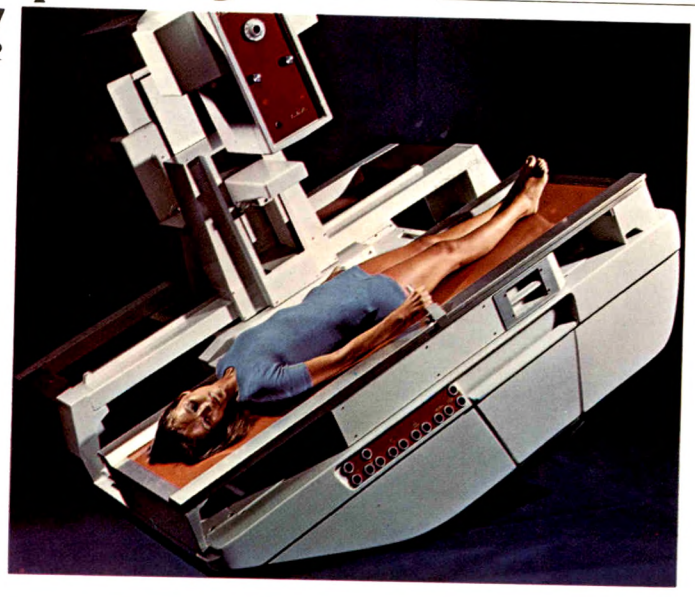

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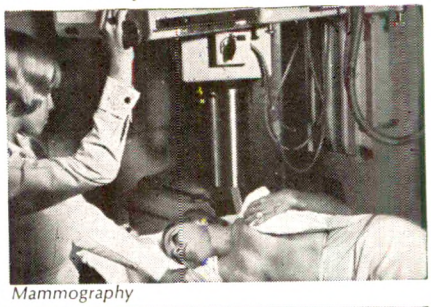

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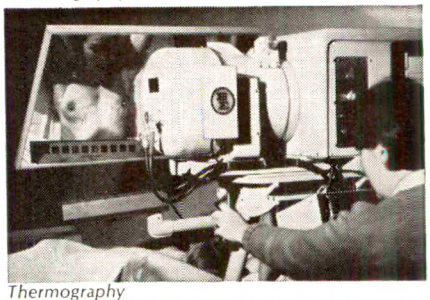

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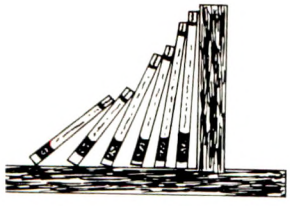

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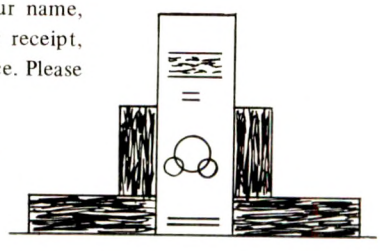

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Smith, John

Xray # 32198

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Dr. N. Hall
Received: 11:20 AM Monday, May 21st, 1973

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1:04 PM Monday, May 21st, 1973

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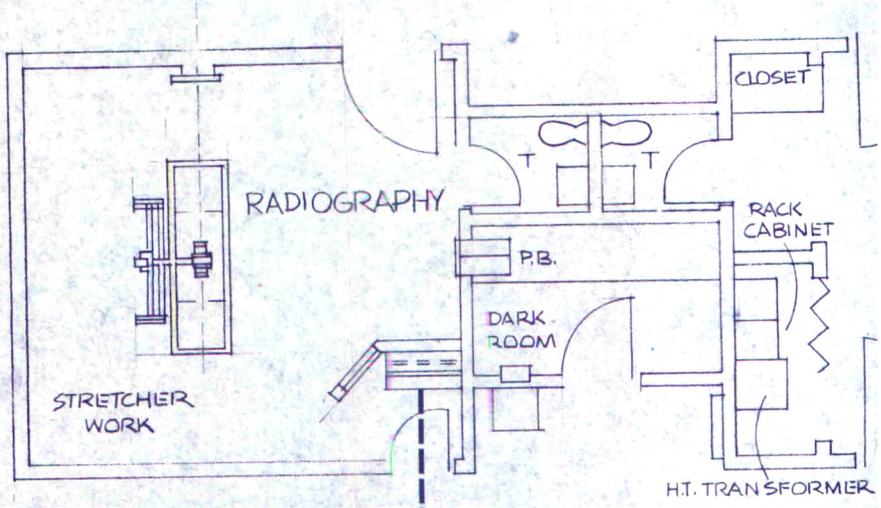

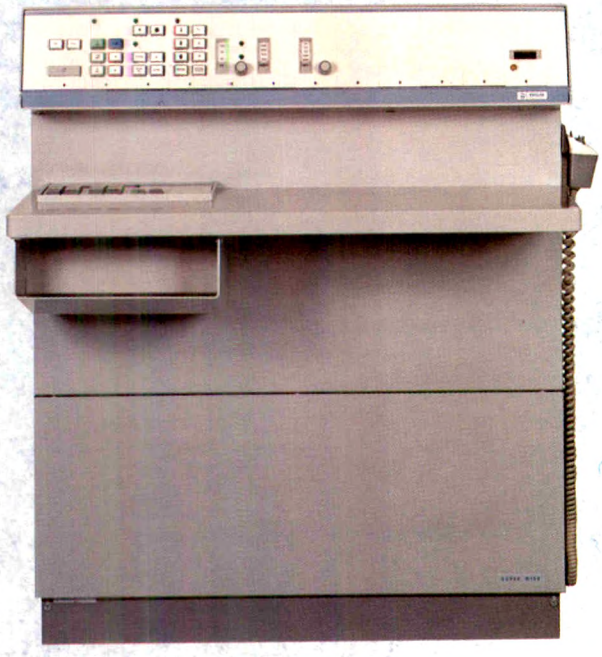

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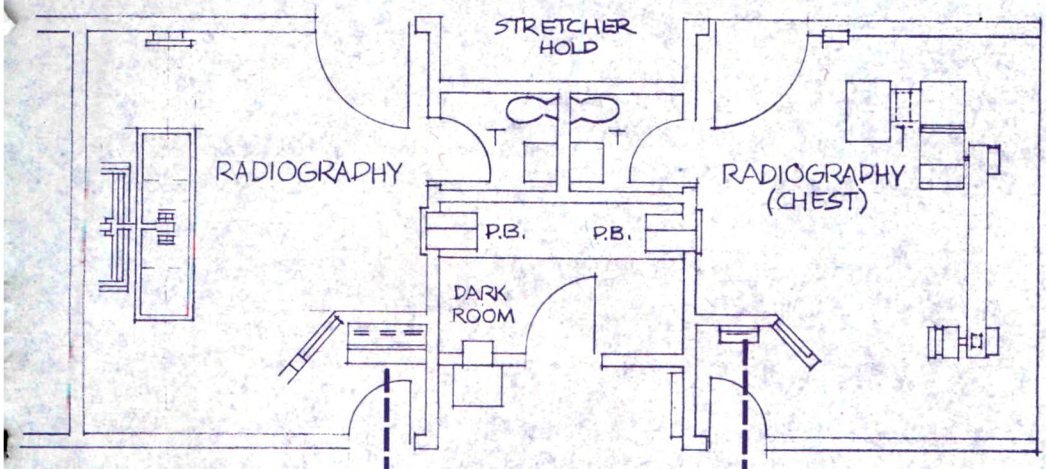

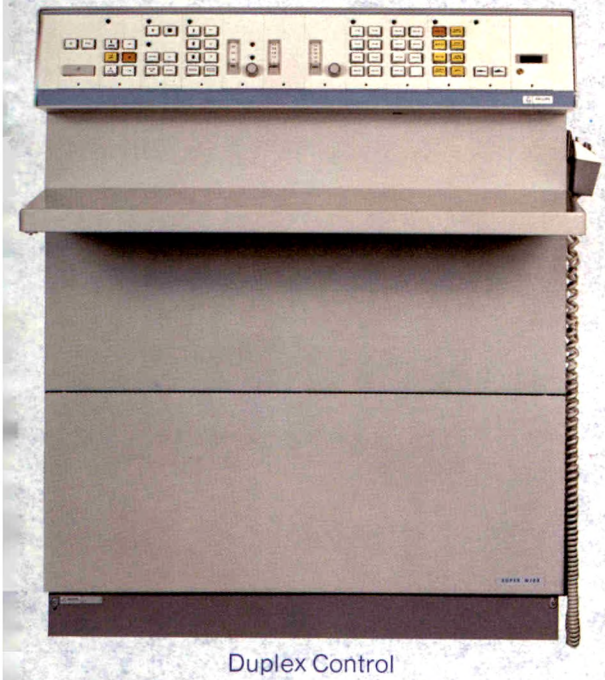

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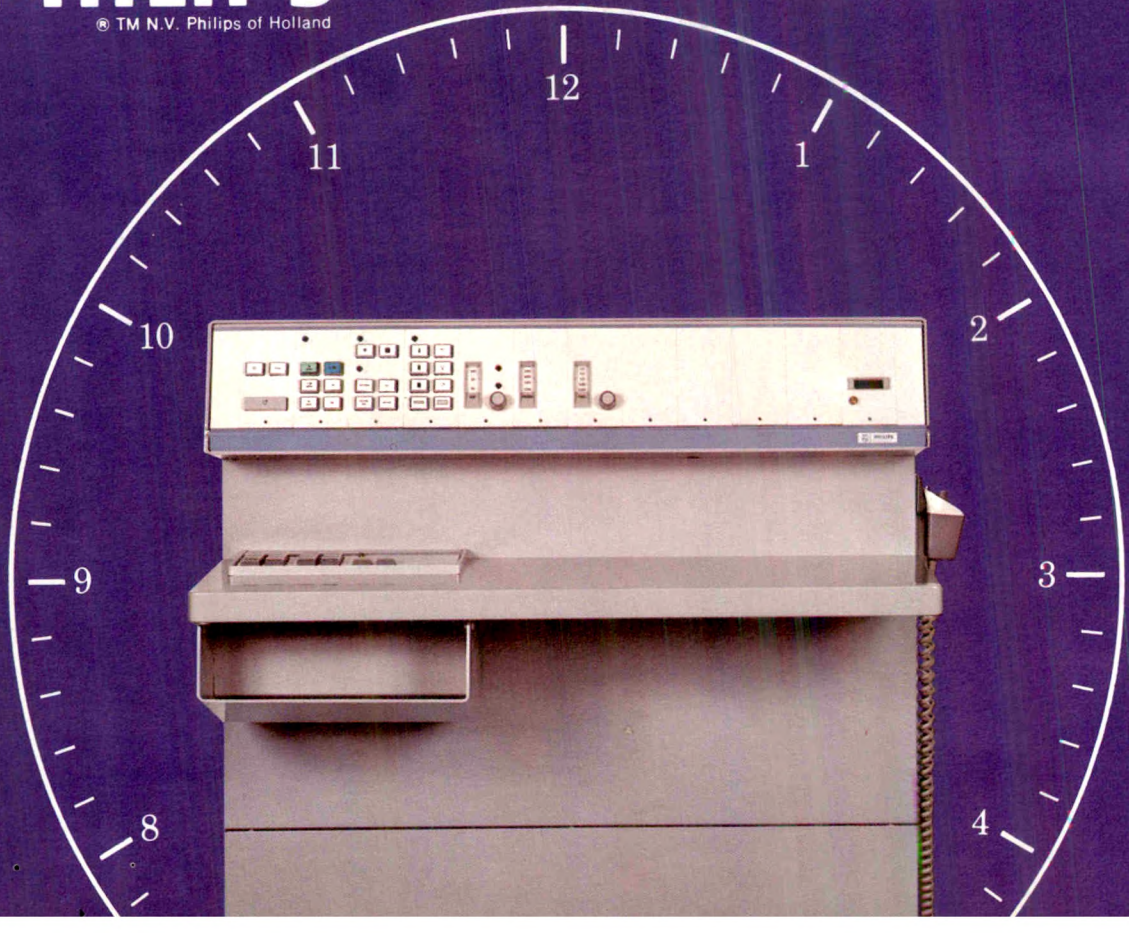

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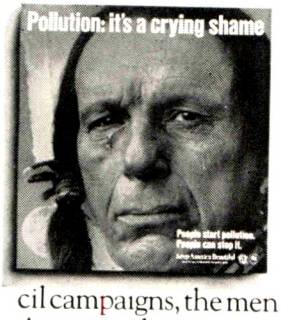

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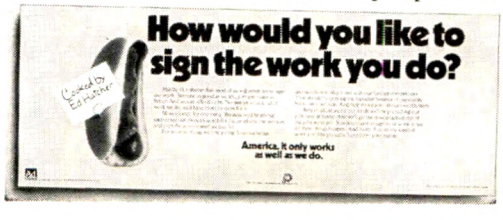

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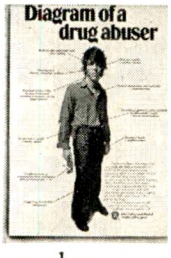

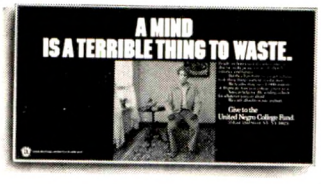

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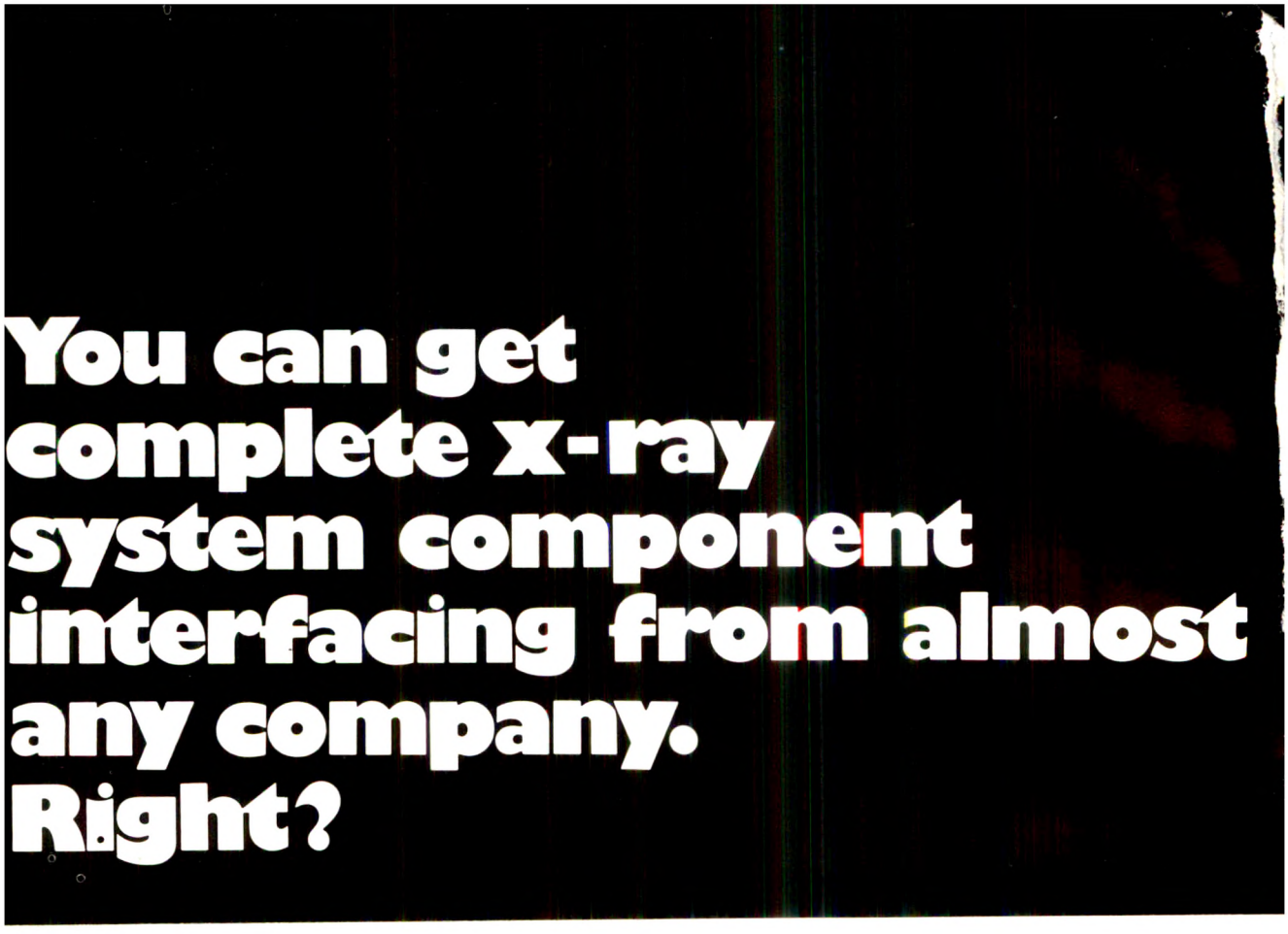

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